

A Collection of

NIDA NOTES

**NATIONAL INSTITUTE
ON DRUG ABUSE**

Articles That Address



**RESEARCH
ON NICOTINE**

**Department of Health and Human Services
National Institutes of Health
National Institute on Drug Abuse**

Introduction

The National Institute on Drug Abuse (NIDA) supports more than 85 percent of the world's research on drug abuse and addiction. NIDA-funded research enables scientists to apply the most advanced techniques available to the study of every aspect of drug abuse, including:

- genetic and social determinants of vulnerability and response to drugs;
- short- and long-term effects of drugs on the brain, including addiction;
- other health and social impacts of drug abuse, including infectious diseases and economic costs;
- development and testing of medication and behavioral treatments for abuse and addiction; and
- development and evaluation of effective messages to deter young people, in particular, from abusing drugs.

Included in this document are selections of topic-specific articles reprinted from NIDA's research newsletter, *NIDA NOTES*. Six times per year, *NIDA NOTES* reports on important highlights from NIDA-sponsored research, in a format that specialists and lay readers alike can read and put to use. Selections like the current one are intended to remind regular *NIDA NOTES* readers and inform other readers of important research discoveries during the periods they cover.

We hope the information contained here answers your needs and interests. To subscribe to *NIDA NOTES* and for further information on NIDA's drug abuse and addiction research, please visit our Web site at www.drugabuse.gov.

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Nicotine Disrupts Brain Development in Rats

By Patrick Zickler, *NIDA NOTES* Staff Writer

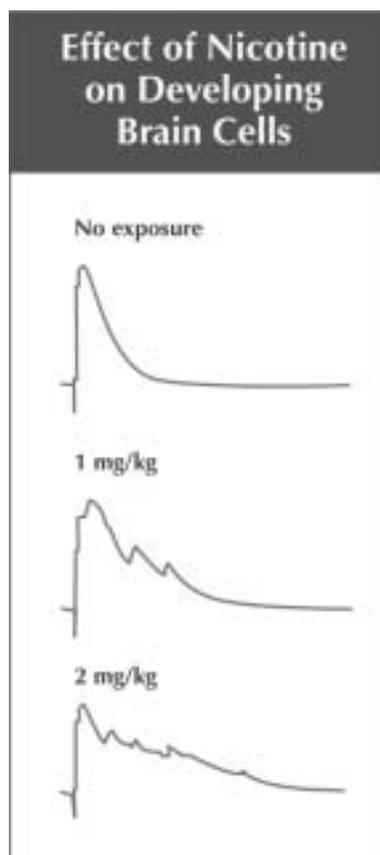
Exposure to nicotine during a brief but crucial stage of brain development in rats appears to cause long-lasting disruption of some brain functions. NIDA-supported researchers Dr. Frances Leslie, Dr. Raju Metherate, and colleagues at the University of California, Irvine, found that nicotine injected into rats throughout the second postnatal week affected development of an area of the brain that is concerned with the interpretation of sounds, and that the effects persisted for at least 10 days after nicotine injections were discontinued.

"There are critical periods during which nicotine exposure can produce profound changes in brain function," Dr. Leslie says. "Our study suggests that the nicotine content of tobacco triggers responses in developing brains that are strikingly different from those in an adult brain."

In rats, there is a dramatic increase during the second postnatal week in the number of nicotinic acetylcholine receptors—brain cell structures that are sensitive to nicotine and help regulate the action of the chemical messenger acetylcholine. Developments in the rat brain during this period correspond to changes that take place in human fetuses during the last weeks of gestation.

To evaluate the effect of nicotine during this period of brain development, the researchers injected rat pups twice each day with saline or with nicotine (1 or 2 mg per kilogram of body weight—levels typically used by researchers to simulate exposure levels thought to occur in human fetuses due to maternal smoking) for 1 week (postnatal days 8 through 14). Two other groups of rats received injections (2 mg/kg) on postnatal days 1 through 8 and on postnatal days 20 through 25, respectively. The researchers then measured electrical properties of brain cells in the auditory cortex to determine the cells' ability to properly process electrical signals involved in hearing. They found that cells from animals exposed to nicotine—at doses of 1 or 2 mg/kg—during the second postnatal week had significant impairment while those exposed to the higher dose earlier or later did not.

"Together, these findings indicate that chronic nicotine exposure during week 2, but not before or after, alters development in the auditory cortex of rats," Dr. Leslie says. The resulting defects do not impair the animals' ability to distinguish sounds—they are not hard of hearing—but the defects make the rats less able to associate sounds,



To determine the effect of nicotine on developing brains in the auditory cortex (the part of the brain where sounds are associated with meanings), researchers measured an electrical property (excitatory postsynaptic potential or EPSP) that influences the transmission of signals from one nerve cell to another. In animals not exposed to nicotine (top), neurons exhibited smooth short-duration EPSPs. Nerve cells from animals exposed daily to nicotine at doses of 1 mg/kg (middle) and 2 mg/kg (bottom) during the second week after birth exhibited longer duration EPSPs marked by frequent spikes, which interfere with effective transmission.

such as the yips of littermates, with specific activities such as feeding, according to the researchers. "In humans, maternal smoking has been associated with cognitive deficits in infants, and particularly with auditory-related cognitive impairments such as reduced ability to orient toward clearly heard sounds. This animal study suggests a mechanism that might underlie these impairments," Dr. Leslie says.

Source

- Aramakis, V.B.; Hsieh, C.Y.; Leslie, F.M; and Metherate, R. A critical period for nicotine-induced disruption of synaptic development in rat auditory cortex. *Journal of Neuroscience* 20(16):6106-6116, 2000. **NN**

Adolescents, Women, and Whites More Vulnerable Than Others to Becoming Nicotine Dependent

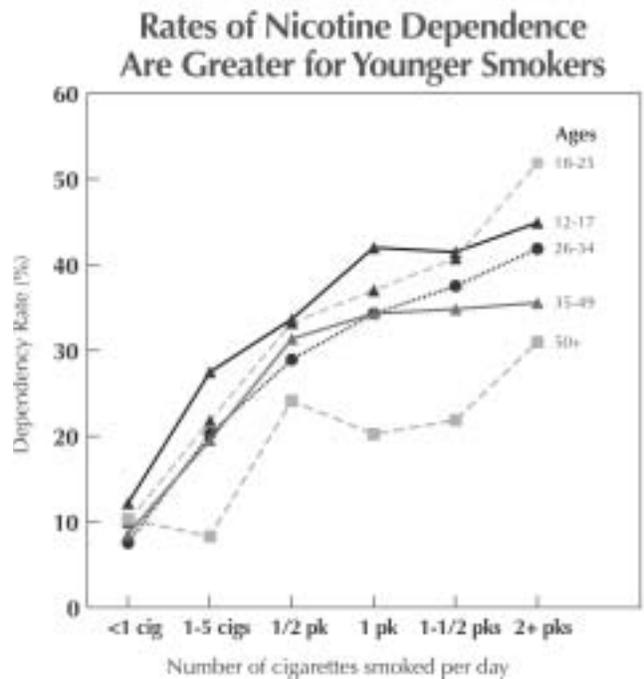
By Patrick Zickler, NIDA NOTES Staff Writer

Rates of drug dependence—the percentage of users who experience symptoms that reinforce their drug use and have trouble quitting—are higher for nicotine than for marijuana, cocaine, or alcohol. Rates of dependence also vary among different groups of smokers, according to NIDA-supported research. A new study suggests that differences in sensitivity to nicotine make some smokers more likely than others to develop nicotine dependence. Age, sex, and race all appear to make a difference.

Dr. Denise Kandel and Dr. Kevin Chen of Columbia University in New York City analyzed data collected between 1991 and 1993 as part of the National Household Survey of Drug Abuse, which surveys a representative sample of the U.S. population 12 years and older. In examining data from 22,292 respondents who had smoked cigarettes during the preceding month, Dr. Kandel and her colleagues determined rates of nicotine dependence symptoms based on respondents' reports of tolerance (needing to smoke more to feel the effects), withdrawal symptoms, smoking more than intended, failed efforts to cut down, negative social and job-related consequences, and persistent health problems.

The researchers found that among persons who smoke one-half pack of cigarettes each day, nicotine dependence rates are higher among females than males (31.6 percent compared with 27.4 percent) and higher among whites (31.3 percent) than among blacks (25 percent) and Hispanics (27.6 percent). Adolescents smoke fewer cigarettes than adults but experience significantly higher rates of dependence than adults at the same level of use. Dependence rates are lowest among adults older than 50. Overall, the researchers say, dependence rates increase sharply as consumption moves up to 10 cigarettes per day. The rates level off with higher consumption, although dependent smokers need to smoke more to feel the physical effects of nicotine.

"Understanding the differences among groups in their vulnerability to developing nicotine dependence will be valuable in developing targeted strategies for prevention," Dr. Kandel says. "The higher rates at which adolescent, women, and white smokers develop symptoms of nicotine dependence given the same quantity smoked daily seem to



Data from the National Household Survey on Drug Abuse show that the rate of nicotine dependence is higher in people younger than 25 than in other age groups and that the dependence develops with less exposure to nicotine.

reflect differences in sensitivity to nicotine. Increased sensitivity may also account for the fact that adolescents develop symptoms of dependence at lower doses of nicotine than adults."

Adolescents appear to be particularly vulnerable to becoming nicotine dependent, especially at low levels of cigarette consumption and when they continue to smoke on a regular daily basis, according to the researchers. Adolescents' nicotine dependence rates were associated with the length of time that they had been daily smokers, in contrast with adults, in whom dependence rates were associated with the amount of tobacco smoked. "Once regular smoking has been established, quantity smoked may become a

more important determinant of dependence than duration of daily smoking," Dr. Kandel says. "This possible connection suggests that with adolescents we should focus not only on preventing the uptake of smoking but on shortening smoking careers as soon as possible."

Source

- Kandel, D.B., and Chen, K. Extent of smoking and nicotine dependence in the United States: 1991-1993. *Nicotine and Tobacco Research* 2(3):263-274, 2000.
NN

Maternal Smoking During Pregnancy Associated With Negative Toddler Behavior and Early Smoking Experimentation

By Josephine Thomas, *NIDA NOTES* Contributing Writer

NIDA-funded researchers have added to the accumulating scientific evidence that women's smoking during pregnancy adversely affects their children's health and development. Two new studies have linked prenatal tobacco exposure to negative behavior in toddlers and smoking experimentation by pre-adolescents. In a study conducted by Dr. Judith Brook, Dr. David Brook, and Dr. Martin Whiteman of the Mount Sinai School of Medicine in New York City, mothers who smoked during pregnancy indicated that their toddlers exhibited more negative behaviors—impulsiveness, risk-taking, and rebelliousness—than mothers who did not smoke during pregnancy reported among their children.

A study conducted by NIDA-funded researchers Dr. Marie Cornelius and Dr. Nancy Day demonstrates that, even more than growing up in a home where the mother smokes, prenatal exposure to smoke may predispose children to early smoking experimentation. Dr. Cornelius, Dr. Day, and their colleagues at the University of Pittsburgh School of Medicine found that not only does such exposure to maternal smoking predict early experimentation, it also appears linked to child anxiety, depression, and behaviors such as hitting and biting others.

Previous studies have supported a link between prenatal smoking exposure and behavioral problems in later childhood and adolescence (see "Drug Abuse and Conduct Disorder Linked to Maternal Smoking During Pregnancy," V15-5, October 2000.) Combined with earlier results, the new studies suggest that prenatal smoking contributes to a train of developmental difficulties and health risks that begin at an early age.

Toddler Negativity

The Mount Sinai study included 99 mothers who smoked and their 2-year-old children. The mothers are participants in a large community study that Dr. Judith Brook has been conducting with Dr. Patricia Cohen of Columbia University in New York City for the past 25 years. In the



new study, the mothers answered a questionnaire that elicited information about their children's behaviors and their own smoking histories, alcohol and drug use, personalities and attitudes, styles of child-rearing, and socioeconomic characteristics.

Fifty-two of the women reported that they had smoked while pregnant, and 47 said they either stopped smoking during pregnancy or did not begin to smoke until after they had given birth. The mothers who smoked during pregnancy scored their children higher on the questions that measured toddler negativity. The mother's disciplinary style also was strongly linked to a toddler's negative behavior. However, when the researchers adjusted for this factor in the analysis, they

determined that a mother's smoking during pregnancy independently increased the estimated risk of negativity at age 2 by fourfold.

"We found three major maternal risk factors related to toddler negativity," says Dr. Brook. "They are maternal smoking during pregnancy, conflicts between the mother and child, and the mother's use of power-assertive discipline, such as hitting the child. We can speculate that maternal smoking during pregnancy causes disturbances in the neurophysiological functioning of the fetus," says Dr. Brook. "This, in turn, could precipitate the toddler's negative behavior."

The potential implications of these findings reach beyond early childhood. Previous studies have demonstrated that toddlers who display negative behaviors are more likely to use drugs, exhibit delinquent behaviors, and achieve less as adolescents and to develop severe mental health problems later in life.

Early Experimentation With Tobacco

Although the effects of maternal smoking on childhood behaviors have been studied, few studies have investigated the connection between maternal smoking and childhood

experimentation with tobacco. The connection is important because the earlier a person starts smoking, the more likely he or she is to become a regular smoker, become addicted, and suffer the long-term adverse health effects of smoking.

Dr. Cornelius and her colleagues interviewed 589 10-year-olds. Six percent of the children said they had tried cigarettes, smokeless tobacco, or both. Most of the reported tobacco use was experimental; only a few children had used tobacco more than a few times.

In this prospective study, begun by Dr. Day in 1982, the children's mothers have been providing researchers with information about themselves, and they reported on their smoking at the time they were pregnant with the children who are now 10. Putting data from the children together with those reports, the researchers estimated that maternal smoking of at least a half-pack of cigarettes per day during pregnancy increased by fivefold the likelihood that a child would have tried tobacco by age 10. The only factor that produced a greater risk of early experimentation was exposure to smoking within the child's peer group.

It is not yet clear exactly why these factors are related to early experimentation. "Perhaps the nervous system damage caused by maternal smoking may later be expressed as

impulsivity, inattention, aggression, depression, and/or anxiety and may create a vulnerability in the child that could contribute to poorer adjustment and an increased likelihood of early initiation of tobacco use,"

Dr. Cornelius says.

Dr. Cornelius notes that in her study, the 10-year-olds who were exposed prenatally to tobacco were more likely to have experimented than those whose mothers were current smokers. This finding reinforces the hypothesis that a physiological effect of prenatal exposure to smoking, rather than a genetic vulnerability affecting both mother and child, may be an important link between mothers' smoking during pregnancy and early childhood experimentation.

Sources

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- Cornelius, M.D.; Leech, S.L.; Goldschmidt, L.; and Day, N.L. Prenatal tobacco exposure: Is it a risk factor for early tobacco experimentation? *Nicotine & Tobacco Research* 2:45-52, 2000. **NN**

Smoking May Lead to Anxiety Disorders in Adolescents and Young Adults

Using a wealth of data obtained through a 25-year longitudinal study, NIDA-funded researcher Dr. Judith Brook of the Mount Sinai School of Medicine in New York, Dr. Patricia Cohen of Columbia University in New York, and their colleagues have documented adverse effects of smoking in several critical areas of functioning during young adulthood. Most recently, the team has reported a connection between tobacco use by adolescents and young adults and the likelihood that they will develop agoraphobia (fear of leaving home or of the outdoors), generalized anxiety disorder, or panic disorder. Analyzing data from their Children in the Community study, funded by NIDA and the National Institute of Mental Health, the researchers were able to separate the effects of smoking from the effects of age, gender, childhood temperament, alcohol and other drug abuse, and depression among the adolescents, as well as parents' smoking, education, and behavioral and/or mental health problems.

The researchers interviewed 688 youths and their mothers in 1983, between 1985 and 1986, and again between 1991 and 1993. A total of 69 of the youths smoked heavily—at least 20 cigarettes every day—and experienced an anxiety disorder during adolescence, early adulthood, or both. Of these 69 youths, 29 (42 percent) began smoking before they were diagnosed with an anxiety disorder. The remaining 40 youths were split between those who were diagnosed with anxiety disorders before they reported heavy smoking (13, or 19 percent) and those who

reported smoking and were diagnosed with anxiety disorders at the same interview session (27, or 39 percent).

Adolescents who smoked heavily were 6.8 times more likely to develop agoraphobia, 5.5 times more likely to develop generalized anxiety disorder, and 15.6 times more likely to develop a panic disorder as young adults than were their counterparts who smoked fewer than 20 cigarettes a day or not at all. The investigators speculate that impaired respiration and the potentially damaging effects of nicotine on blood vessels to the brain may help explain why the adolescents who smoked heavily were at increased risk of developing anxiety disorders.

The long-held notion that depression causes some adolescents to smoke may be true. But Dr. Brook's study suggests the opposite may also be true—that smoking increases the risk of depression in this population. Dr. Brook and her team recommend that future research examine further the possible relationships between various anxiety disorders and smoking.

Source

- Johnson, J.G.; Cohen, P.; Pine, D.S.; Klein, D.F.; Kasen, S.; and Brook, J.S. The association between cigarette smoking and anxiety disorders during adolescence and early adulthood. *Journal of the American Medical Association* 284(18):2348-2351, 2000. **NN**

Nicotine Patch Helps Smokeless Tobacco Users Quit, But Maintaining Abstinence May Require Additional Treatment

By Robert Mathias, *NIDA NOTES* Staff Writer

An estimated 9.6 million people in the United States used smokeless tobacco products—moist snuff and chewing tobacco—during 1998, according to the National Household Survey on Drug Abuse. More than 70 percent of these individuals had used smokeless tobacco during the month before they were surveyed.

People who are trying to quit using smokeless tobacco may benefit from a transdermal nicotine patch during the first critical months after stopping use, a NIDA-supported study suggests. Study participants treated with the nicotine patch experienced less severe withdrawal symptoms and lower levels of craving for nicotine and were significantly more likely to maintain short-term abstinence than users in a control group who were treated with an inactive patch. Treatment with nicotine-free mint snuff also reduced withdrawal symptoms and craving but had no effect on abstinence rates.

"These findings suggest that the nicotine patch can reduce the discomfort that people experience when quitting smokeless tobacco," says Dr. Dorothy Hatsukami of the University of Minnesota School of Medicine, who conducted the study. "Knowing that withdrawal symptoms can be minimized may encourage more people to try to quit," she says. While the study suggests that the nicotine patch may help patients achieve initial abstinence from smokeless tobacco, it remains unclear how the patch and other treatments should be used to sustain abstinence over the long term, she says.

Most tobacco-related research has focused on cigarette smoking with its more extensive range of harmful consequences, Dr. Hatsukami says. "However, we also need to study smokeless tobacco use because it is not an insignificant problem by any means," she says. Regular use of



smokeless tobacco products may cause such problems as receding gums, tooth decay, mouth sores, precancerous lesions, and cancers of the mouth and throat. Smokeless tobacco users also may be at increased risk of heart disease and smoking cigarettes. Undesirable social consequences include bad breath, tobacco-stained teeth, and the need to spit tobacco juice.

Many individuals use smokeless tobacco despite its obvious drawbacks because they are hooked on nicotine, a highly addictive drug. As with cigarettes, smokeless tobacco products deliver substantial doses of nicotine along with powerful cancer-causing chemicals. Users of moist snuff—which consists of finely ground tobacco—place a pinch, or dip, of snuff between their cheek and gum and hold it there. Users of chewing tobacco—which comes in leaf and plug forms—place a wad, or chew, in their cheek pouch and chew it. Because nicotine from smokeless tobacco is absorbed through the mouth, the drug takes longer to produce its

rewarding effect in the brain than it does when it is absorbed through the lungs during cigarette smoking. The amount of nicotine obtained from smokeless tobacco is comparable to that of cigarettes, and once smokeless tobacco users become addicted they find it just as difficult as cigarette smokers do to quit, Dr. Hatsukami says. She notes that more than 90 percent of the smokeless tobacco users in her study had tried unsuccessfully to quit on their own at least once. Nearly 25 percent of the study's participants had made more than 6 unsuccessful quit attempts, and nearly 10 percent had tried to quit more than 10 times.

In her study, Dr. Hatsukami randomly assigned a total of 402 smokeless tobacco users to one of 4 treatments: active

nicotine patch, inactive patch, a combination of active patch and a non-nicotine mint snuff, or a combination of inactive patch and mint snuff. All participants received initial counseling on smokeless tobacco cessation methods and a self-help manual to take home prior to beginning treatment. On their quit date,

patients began using their assigned treatments and continued for 10 weeks. During treatment, participants met weekly with counselors for brief support sessions. Results were assessed 15, 25, 36, and 62 weeks after participants stopped using smokeless tobacco. The study found that both the active patch and mint snuff reduced craving and withdrawal symptoms, such as irritability, frustration, anger, anxiety, and depressed mood. Withdrawal symptoms generally peaked during the first week after use was stopped. Only the active patch improved rates of continuous abstinence at 10 and 15 weeks following cessation. By the 23rd week, the differences in abstinence rates among all treatments had become marginal, although active patch users were still slightly more likely to be abstinent. At 62 weeks following cessation, no significant differences in abstinence were observed for any of the treatment conditions.

"A number of studies have shown that the nicotine patch is more effective than a placebo patch in sustaining long-term abstinence from cigarette smoking, but the patch appeared to be effective with smokeless tobacco users only during the period of actual patch use and shortly thereafter," notes Dr. Hatsukami. "We don't know if this

Many individuals use smokeless tobacco despite its obvious drawbacks because they are hooked on nicotine, a highly addictive drug.

means we need to use the patch for longer periods of time with smokeless tobacco users or if sensory or behavioral aspects of smokeless tobacco use, such as putting something in one's mouth, may be as important as the nicotine in sustaining use," she says. The fact that a nicotine-free mint snuff also reduced withdrawal symptoms illustrates the

potential importance of the sensory aspects of smokeless tobacco in sustaining its use, she says. Previous research does suggest that intensive, multicomponent, behavioral treatment may help smokeless tobacco users to sustain abstinence over the longer term, she says.

"Many questions about smokeless tobacco use and its treatment remain unanswered," Dr. Hatsukami says. "We really need to learn more about all the dimensions of smokeless tobacco use to develop effective treatments that are better tailored to this underserved population," she says.

Sources

- Hatsukami, D.K., et al. Treatment of spit tobacco users with transdermal nicotine system and mint snuff. *Journal of Consulting and Clinical Psychology* 68(2):241-249, 2000.
- Hatsukami, D.K., and Severson, H. Oral spit tobacco: addiction, prevention and treatment. *Nicotine and Tobacco Research* 1(1):21-44, 1999. **NN**

Women and Smokeless Tobacco Use

Although more than 90 percent of smokeless tobacco users in the United States are male, a substantial number of women also use smokeless tobacco products. In 1998, 0.5 percent of females over the age of 12, about 573,000, were current users of smokeless tobacco products, according to the National Household Survey on Drug Abuse.

The comparatively small percentage of women who use smokeless tobacco accounts in part for the lack of research on the patterns of smokeless tobacco use among women, says Dr. Dorothy Hatsukami of the University of Minnesota School of Medicine. In addition, "women rarely respond to our advertisements to participate in smokeless tobacco treatment studies," she says. For example, Dr. Hatsukami recently reported that 99.8 percent of 402 people who responded to advertisements for participation in a smokeless tobacco treatment study with the nicotine patch were male. (See "Nicotine Patch Helps Smokeless Tobacco Users Quit, But Maintaining Abstinence May Require Additional Treatment.")

"Women may be embarrassed about admitting smokeless tobacco use because the general perception is that smokeless tobacco use is socially undesirable, and women don't use it," Dr. Hatsukami speculates. Among the unattractive features of smokeless tobacco use is the need to spit tobacco juice from time to time and dislodge particles of loose tobacco that get trapped between the teeth. This disadvantage of smokeless tobacco use was the one most frequently cited by women who participated in a study of female smokeless tobacco users who weren't seeking treatment, conducted by Dr. Hatsukami and her colleagues.

In the study, 20 female smokeless tobacco users from the upper Midwest completed a questionnaire and brief interview. The study revealed some similarities between females' smokeless tobacco use and what research has shown about males' smokeless tobacco use. For example, on average, both sexes began using smokeless tobacco between 16 and 18, and friends played a major role in their initiating use. About 25 percent of men and women also indicated they used smokeless tobacco to help them stop smoking.

The study also revealed some differences in patterns of smokeless tobacco use by females and the patterns of use reported in a previous study that assessed features of smokeless tobacco use among males who weren't seeking treatment. For example, on average, the women said they

used 3.6 dips of moist snuff daily, compared to the 6.3 dips reported by males, and women held the tobacco in their mouths about 22.5 minutes, compared to 39.9 minutes for men. A tin of snuff lasted women anywhere from 2 days to 3 months with a median duration of 6 days per tin. In contrast, men used approximately 2.8 tins per week.

The women in this study may have used less smokeless tobacco than men because they had used smokeless tobacco for less than 4 years, Dr. Hatsukami says. This contrasts with the men, who averaged more than 5 years of smokeless tobacco use. Perceived social disapproval of women using smokeless tobacco also may contribute to lower patterns of use in women. In fact, 38 percent of the women in Dr. Hatsukami's study said they could not use smokeless tobacco in the presence of certain people, and another 25 percent cited social disapproval as a drawback to smokeless tobacco use. These social concerns may reduce opportunities for women to use smokeless tobacco and lead to lower levels of use, Dr. Hatsukami says. In spite of these drawbacks, a significant percentage of women in the study said the relaxing and calming effects and pleasure they associate with smokeless tobacco use are advantages of using these products.

Identifying factors associated with smokeless tobacco use by women and their current patterns of use could generate ways to prevent and treat smokeless tobacco use among women, Dr. Hatsukami says. "The data from this research could help target some of the educational and prevention messages that we should be giving to women," she says. "However, first we have to make women smokeless tobacco users aware that other women use smokeless tobacco products and that they are not abnormal, so they are willing to seek help," she says.

Sources

- Boyle, R.G.; Gerend, M.A.; Peterson, C.B.; and Hatsukami, D.K. Use of smokeless tobacco by young adult females. *Journal of Substance Abuse* 10:19-25, 1998.
- Hatsukami, D.K.; Keenan, R.M.; and Anton, D.J. Topographical features of smokeless tobacco use. *Psychopharmacology* 96:428-429, 1988. **NN**

NIDA's Nicotine Research Featured at World Tobacco Conference

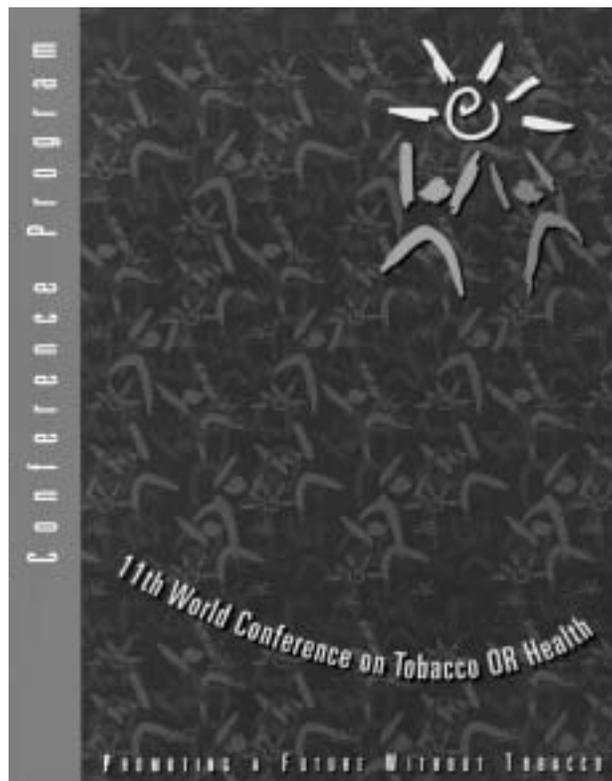
By Patrick Zickler, NIDA NOTES Staff Writer

More than 4,000 attendees at the 11th World Conference on Tobacco OR Health heard NIDA Director Dr. Alan I. Leshner and NIDA-supported researchers from the United States and Canada describe the Institute's portfolio of scientific research into the nature of tobacco use and nicotine addiction.

The conference, held every 3 years, brings together scientists, health care providers, public policy officials, and tobacco control advocates from more than 100 countries to promote comprehensive efforts to reduce tobacco use. The conference met in Chicago in August, marking the first time in 25 years that the meeting has been held in the United States. NIDA served as a contributing partner to the conference, which was sponsored by the American Cancer Society, the American Medical Association, and The Robert Wood Johnson Foundation.

"The past decade has brought a revolution in our understanding of nicotine addiction and of all addictions," Dr. Leshner told a plenary session of the conference. "We have built a solid foundation of knowledge about why people smoke, why it is so very hard to stop, and how pharmacological and behavioral treatment can help smokers overcome their destructive addiction to nicotine," Dr. Leshner said.

In other conference sessions, NIDA-supported investigators described current research into the genetic and neurobiological characteristics of nicotine addiction, new imaging techniques to improve understanding of the drug's mechanisms of action, and progress in the development of pharmacological treatments such as vaccines and medications to reduce nicotine's addictive effects.



One symposium focused on the role of genetic factors in nicotine addiction and ways in which this improved understanding of genetic influences can contribute to development of more effective prevention and treatment. Dr. Kathleen Merikangas of Yale University in New Haven, Connecticut, discussed research that reveals intergenerational and other familial patterns of smoking behavior. Dr. Andrew Heath of the Washington University School of Medicine in St. Louis described genetic factors that influence nicotine metabolism and make some individuals less likely to begin smoking and more successful in quitting. Dr. Rachel Tyndale of the University of Toronto reviewed progress in the identification of medica-

tions that can reduce susceptibility to nicotine by reducing nicotine metabolism. (See "Evidence Builds That Genes Influence Cigarette Smoking," V15-2, August 2000, and "NIDA-Funded Researchers Identify Compound That Inhibits Nicotine Metabolism, Decreases Urge to Smoke," V15-5, October 2000.)

NIDA Associate Director Dr. Timothy P. Condon and Dr. Jaylan Turkkan, chief of NIDA's Behavioral Sciences Research Branch, chaired a symposium on addiction science, which provided a look at the broad range of NIDA's nicotine research portfolio. Dr. Frances Leslie of the University of California, Irvine, described animal studies that have identified the critical periods in brain development when exposure to nicotine can produce dramatic and long-lasting changes in brain function. These findings, she said, suggest that children's brains may respond to nicotine exposure in a way that is strikingly different from the response of adults. Dr. Paul Pentel of the

Hennepin County Medical Center in Minneapolis discussed progress on the development of a vaccine that could bind to nicotine molecules in the blood, preventing the biological and behavioral effects that nicotine produces in the brain. (See "Nicotine Vaccine Moves Toward Clinical Trials," V15-5, October 2000.) Dr. Elliot Stein of the Medical College of Wisconsin in Milwaukee described studies that employ functional magnetic

resonance imaging to identify regional brain activity associated with the effects of nicotine. Dr. Kenneth Perkins of the University of Pittsburgh discussed the ways in which long-term individual differences such as sex and genetics, intermediate-term differences such as tolerance to nicotine, and short-term differences such as stress or physical activity combine to determine variations in the way in which nicotine affects individuals. **NN**

Nicotine Vaccine Moves Toward Clinical Trials

By Barbara Shine, NIDA NOTES Staff Writer

A new vaccine that prevents nicotine from reaching the brains of rats may offer hope for smokers trying to break their addiction. The compound, called NicVAX, may even prove useful as an inoculation against nicotine addiction, much like those that protect children from tetanus, measles, and polio.

"Some form of vaccination against nicotine would be highly useful because vaccinated individuals would not be able to get a 'kick' from the nicotine in tobacco smoke or chewing tobacco," says NIDA Director Dr. Alan I. Leshner. "If people found tobacco less rewarding, they would be less likely to continue using it. Ultimately, however, our best treatment for nicotine addiction is prevention."

NicVAX is manufactured by Nabi, a Florida-based pharmaceutical company that has NIDA grant support to conduct preclinical studies to determine whether the vaccine is toxic to animals and, then, if the compound is proven safe, clinical trials to evaluate its safety and efficacy in humans. The 4-year project begins this fall, and clinical trials are planned for 2002. Primary coinvestigators include Dr. Ali Fattom and other Nabi scientists in Rockville, Maryland, as well as the Minnesota- and Texas-based researchers who conducted the early animal studies.

Paul Pentel and his colleagues at the Minneapolis Research Foundation and Hennepin County Research Center in Minneapolis and Dr. David Malin at the University of Houston at Clear Lake tested NicVAX with rats. Injection of NicVAX stimulated antibodies to neutralize nicotine in the blood, reducing by 65 percent the amount of nicotine that reached the animals' brains. The nicotine-specific antibodies produced by NicVAX also reduced the effects of nicotine on blood pressure and the heart.

Now NicVAX is proposed as a therapy that can enhance current treatments for nicotine addiction by helping quitting smokers resist the urge to light up. The hypothesis is that the vaccine may inhibit nicotine's "priming effect"—the phenomenon in which a formerly addicted individual experiences an increased desire to use a drug after a single



Dr. Ali Fattom (left) and Dr. Sham Shirali of Nabi examine a flask of the nicotine preparation used to produce NicVAX. Photo by Jane Barrett, Nabi, Rockville, Maryland.

exposure, which contributes to relapse. A treatment program built around NicVAX might also include supportive counseling and a medication such as bupropion (Zyban) to reduce withdrawal symptoms.

The animal studies suggest the vaccine's potential for preventing addiction in new tobacco users as well. When rats were injected simultaneously with a nicotine solution and the vaccine, the antibodies that reduced nicotine levels in the rat brains also reduced nicotine dependence.

When the nicotine dosing was stopped, the control group, rats injected with nicotine and a placebo solution, showed significantly greater levels of dependence—measured by abstinence signs such as teeth chattering and tremors—than did the rats treated with NicVAX. Rats were exposed to nicotine at levels comparable to 10 packs of cigarettes daily for a week.

Continuing doses of nicotine do not interfere with the vaccine's ability to induce antibodies in the rats. Animals immunized with NicVAX while they were being injected with nicotine still produced nicotine-specific antibodies. Thus it may be possible to vaccinate a smoker while he or she is still using tobacco so that adequate antibodies will be in place at smoking cessation. The vaccine will continue to work during any relapse, inhibiting the pleasurable response that nicotine would otherwise cause. Further, the vaccine never enters the brain and is therefore unlikely to produce neurological side effects.

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NIDA's Nicotine Research Provides Scientific Approaches To Combat a Deadly Addiction

By NIDA Director Dr. Alan I. Leshner

Nicotine addiction takes a terrible toll on American health. More than 430,000 people die in this country each year from smoking-related causes, and the annual cost of these preventable illnesses—in health care expenditures and lost productivity—is more than \$97 billion. Despite growing public awareness of the deadly dangers of tobacco, nearly 3,000 people younger than 18 become smokers every day and, once addicted, find it very difficult to stop.

Over the past decade, NIDA's nicotine-related research has provided crucial insights into the neurobiological and behavioral aspects of nicotine addiction, and this research has led the way to important advances in treating nicotine addiction. For example, NIDA-supported basic science research and clinical pharmacological studies played a major role in the development of nicotine replacement therapy—a skin patch or chewing gum that reduces the physical discomfort of nicotine withdrawal. Our behavioral science research has contributed to the development, testing, and validation of new behavioral therapies to help smokers resist the craving that often defeats the most determined efforts to stop smoking.

Many of the accomplishments of NIDA's nicotine research effort have been incorporated into a new set of recommendations for primary care practitioners, "Treating Tobacco Use and Dependence: A Clinical Practice Guideline." The recommendations, which were released by U.S. Surgeon General Dr. David Satcher in June, are based on an evaluation of nearly 6,000 peer-reviewed research studies. They endorse pharmacotherapies—sustained release bupropion or nicotine replacement therapy by patch, gum, inhaler, or nasal spray—as well as behavioral therapy, counseling, and support programs to help patients overcome their addiction to nicotine. NIDA—along with the National Cancer Institute; the



Over the past decade, NIDA's nicotine-related research has provided crucial insights into the neurobiological and behavioral aspects of nicotine addiction, and this research has led the way to important advances in treating nicotine addiction.

National Heart, Lung, and Blood Institute; the Centers for Disease Control and Prevention; the Agency for Healthcare Research and Quality; The Robert Wood Johnson Foundation; and the University of Wisconsin Medical School's Center for Tobacco Research and Intervention—sponsored development of the guidelines.

The dividends from NIDA's ongoing investment in nicotine research are increasing. For example, investigators at the Minneapolis Medical Research Foundation have developed a vaccine that, in rats, produces nicotine-specific antibodies that reduce by as much as 65 percent the amount of nicotine that passes from the blood to the brain. The vaccine also prevents some of nicotine's cardiovascular effects and reduces the development of nicotine dependence. This research is a promising first step toward development of a medication that could limit the movement of nicotine from the blood to the brain, reducing the "rush" that addicted smokers experience when they light up and

making it easier for them to quit (for more detailed information on this research, see "Nicotine Vaccine Moves Toward Clinical Trials"). Other NIDA-supported researchers have demonstrated important connections between addictions to nicotine and other addictive drugs. This knowledge can help us develop better therapies for patients with multiple addictions (see "Nicotine Craving and Heavy Smoking May Contribute to Increased Use of Cocaine and Heroin"). NIDA's program of research into genetic factors that influence nicotine addiction has identified a genetically determined variation in liver metabolism that significantly decreases the rate at which the body breaks down and eliminates nicotine from the blood. Individuals with this genetic trait are less likely to become addicted to nicotine and more likely to be able to quit if they do become addicted. NIDA-supported researchers

have found a medication—methoxsalen—that inhibits nicotine metabolism in the same way as the genetic variation. Their studies of the effects of methoxsalen in humans suggest the possibility of developing an entirely new approach to pharmacological treatment of nicotine addiction (see "NIDA-Funded Researchers Identify Compound That Inhibits Nicotine Metabolism, Decreases Urge to Smoke").

Earlier this year, NIDA announced a new research program designed to expand our understanding of the basic science that influences neurobiological and behavioral effects of nicotine and other tobacco chemicals. This program will support investigations that further explain the connections between nicotine and regional brain metabolism, the roles of nicotinic receptors and endocrine regulation, genetic contributions to variations in susceptibility to nicotine addiction, and the neurobiological and behavioral components of nicotine craving.

NIDA's scientific inquiries have provided critical insights into numerous discrete features of nicotine addiction. But tobacco use and nicotine addiction are

complex subjects that can only be truly understood as a dynamic interaction of genetic, environmental, neurophysiological, and behavioral effects. To give us the broad

perspective we need to fully understand this interaction, last year NIDA joined with the National Cancer Institute and The Robert Wood Johnson Foundation to create seven Transdisciplinary Tobacco Use Research Centers (TTURCs) devoted to investigating new ways to combat tobacco use and nicotine addiction. The TTURCs represent an important new approach to research. They bring together collaborators who will have the freedom to investigate broad aspects of nicotine addiction, from factors that influence smoking initiation to the function of specific neurochemicals, and to study the issues at levels ranging from molecular genetics to peer interactions.

The deadly effects of nicotine reach from the individual cell to our national health. NIDA is committed to continuing and expanding a program of scientific research that provides comprehensive and detailed knowledge that can be transformed into effective tools to prevent and treat the chronic and catastrophic effects of nicotine addiction. **NN**



An important part of NIDA's mission is dissemination of the knowledge gained through research. NIDA's newest "art card" describes the similarity between nicotine's addictive properties and those of other addictive drugs. The colorful postcards are distributed at restaurants, bookstores, and coffee shops.

Drug Abuse and Conduct Disorder Linked to Maternal Smoking During Pregnancy

By Raymond Varisco, *NIDA NOTES* Contributing Writer

Researchers at Columbia University in New York City have found new evidence that children whose mothers smoke during pregnancy are at much greater risk than other children for drug abuse and conduct disorder. The findings reinforce those of other studies spanning more than 25 years that have shown similar problems associated with prenatal exposure to smoke in children ranging from toddlers through teens. The study also revealed marked gender differences, with girls at significantly increased risk for drug abuse and boys at significantly increased risk for conduct disorder.

The investigators interviewed 147 mother-child pairs 3 times over 10 years, with the children ranging from ages 6 to 23 at the start of the study. Both mothers and children were interviewed on entry into the study, again 2 years after the initial interview, and, finally, about 10 years after the initial interview. Because the researchers followed the children through either adolescence or young adulthood—something few studies have done before—they were able to collect data about whether and when the children began to abuse drugs, says Dr. Myrna Weissman, the study's principal investigator.

Data were gathered on psychiatric and substance abuse disorders of parents; family environmental factors, such as divorce and family discord; and maternal factors, such as alcohol and coffee consumption and postnatal smoking, to rule out other explanations for the presence of drug abuse and conduct disorder.

The researchers found that maternal smoking during pregnancy has long-term effects on children's behavior and health that cannot be explained by any other factor included in the study. Risk for adolescent drug abuse in girls was more than 5-fold higher if their mothers smoked more than 10 cigarettes a day during pregnancy. Among boys whose mothers smoked more than 10 cigarettes a day, risk for the onset of conduct disorder was greater than 4-fold that of boys whose mothers did not smoke, with the increase appearing in boys younger than 13. The drug most frequently abused by both boys and girls was marijuana, and the most frequent combination of drugs abused was marijuana and cocaine. Of the females who abused drugs, 70 percent abused more than one.

Why boys exposed to smoking before birth should be at risk for conduct disorder and girls at risk for drug abuse remains to be understood, Dr. Weissman says. She speculates that the differences may be related to sex differences in prenatal brain development.

Many of the findings of this study are consistent with those of related studies, she notes. Researchers at the University of Chicago also have found a link between maternal smoking during pregnancy and conduct disorder in boys, she says. Likewise, a 1994 study conducted by Dr. Weissman's coinvestigator Dr. Denise Kandel found that maternal smoking during pregnancy increases risk for adolescent-onset smoking in girls. Studies also have found other behavioral problems in children exposed prenatally to smoke. For example, scientists at Massachusetts General Hospital found an association between prenatal exposure to smoke and attention deficit hyperactivity disorder. Similarly, a recent study by Dr. Judith Brook and her colleagues at Mount Sinai School of Medicine in New York City has found negative behavior in 2-year-olds of mothers who smoked during pregnancy.

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NIDA-Funded Researchers Identify Compound That Inhibits Nicotine Metabolism, Decreases Urge to Smoke

By Patrick Zickler, NIDA NOTES Staff Writer

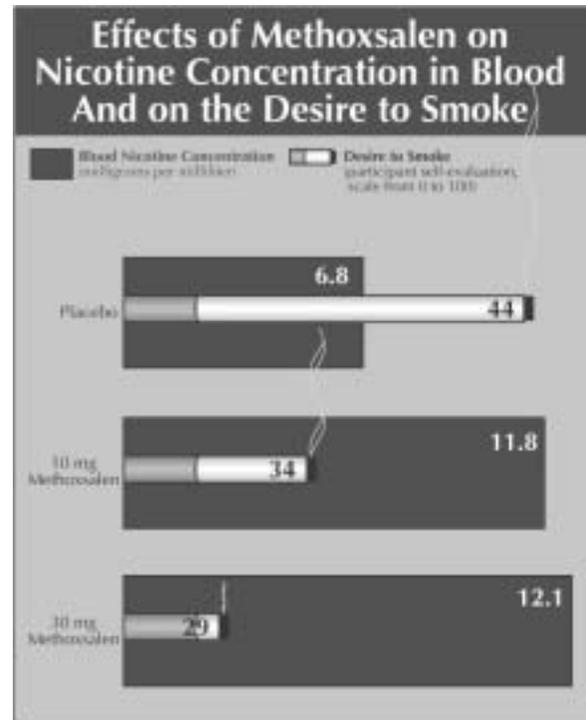
In 1998, NIDA-supported investigators identified a genetic variation that makes some individuals less liable to become addicted to nicotine and, if addicted, more likely to smoke fewer cigarettes and have an easier time quitting than do individuals without the variation. Now the researchers have found that methoxsalen, a medication that mimics the effect of the genetic variation by partially blocking the body's ability to break down nicotine, significantly improves the effectiveness of oral nicotine replacement in reducing a smoker's urge for nicotine. And, according to Dr. Edward Sellers and his colleagues at the University of Toronto, when smokers who receive methoxsalen do light a cigarette, they take fewer and shorter puffs, thereby reducing their exposure to tobacco smoke's carcinogenic components.

"These results suggest that methoxsalen, or other medications that act at the primary site of nicotine metabolism, may represent part of a potent new treatment for nicotine addiction," Dr. Sellers says. "Methoxsalen therapy could reduce smokers' exposure to the harmful constituents of tobacco smoke while serving as part of a step-by-step program of smoking reduction leading to cessation."

Addicted smokers maintain the nicotine in their blood at a concentration that prevents the physical discomfort of withdrawal. They light up a cigarette when that concentration falls. Many smokers who are trying to quit rely on nicotine replacement by transdermal patch or nicotine chewing gum to maintain nicotine levels without smoking. Regardless of the nicotine's source, the drug's blood level falls as it is metabolized by an enzyme produced in the liver, cytochrome P450 2A6 (or CYP2A6).

Dr. Sellers and his colleagues tested more than 200 medications to find compounds that decreased CYP2A6 activity. They found that methoxsalen, which currently is used in treatment regimens for severe psoriasis, reduces the activity of CYP2A6 and makes more nicotine—whether from a cigarette or nicotine replacement—available in the blood for longer. "We found that methoxsalen is a potent CYP2A6 inhibitor," Dr. Sellers says.

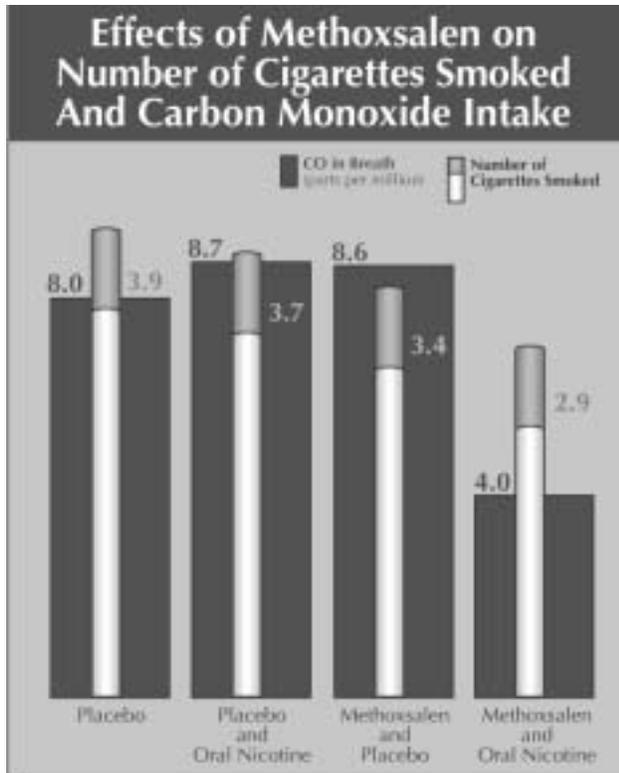
The researchers conducted two studies of methoxsalen's effect on nicotine metabolism and craving for nicotine in smokers with normal CYP2A6 metabolism who were not trying to quit smoking. In one study, 17 smokers (8 men and 9 women) received methoxsalen or placebo



Methoxsalen inhibits the normal liver metabolism of nicotine, and the resulting higher concentration of nicotine in the blood reduces a smoker's desire to smoke. Horizontal bars indicate average blood nicotine concentrations measured 5 times during 3 hours following the administration of oral nicotine combined with placebo or methoxsalen. Cigarettes indicate the participants' desire to smoke, rated from 0 (none) to 100 (strongest).

in combination with oral nicotine replacement. Blood levels of nicotine were measured in samples taken at 30-minute intervals for 3 hours. Participants who received either 10 or 30 milligrams of methoxsalen had mean nicotine levels roughly twice as high as those given placebo. The participants also were asked at hourly intervals to rate their urge to smoke. Those who received methoxsalen reported far less desire to smoke.

In a second study, 11 participants (5 men and 6 women, all of whom had participated in the first study) received either methoxsalen or placebo in combination with nicotine or placebo. Following a 60-minute abstinence, the participants were allowed to smoke at will for 90 minutes.



Participants were allowed to smoke at will for 90 minutes following the administration of combinations of placebo, oral nicotine, and 30 milligrams of methoxsalen.

Participants who received methoxsalen and nicotine had significant reductions in the number of cigarettes smoked and carbon monoxide—one of tobacco smoke's most harmful components—measured in breath.

Smokers who had received methoxsalen plus nicotine smoked fewer cigarettes, had longer intervals between cigarettes, and took fewer puffs on each cigarette.

The doses of methoxsalen used in the studies are lower than the dose approved for human use in treating psoriasis, Dr. Sellers says, but the medication has not been proven safe for long-term use in humans. "We need to establish methoxsalen's safety and efficacy in chronic use before it could be used as part of any smoking cessation treatment," he says.

Methoxsalen offers several advantages as a part of treatment for smoking cessation, Dr. Sellers says. For example, it would make possible the use of a pill, rather than a patch or gum, for nicotine replacement. "Most patients prefer taking an oral medication, and there are places where gum is not appropriate," he says. And, because methoxsalen eliminates almost completely the activity of CYP2A6, which varies from person to person, its use with a nicotine pill could result in more predictable response to nicotine replacement than is possible with either patch or gum, Dr. Sellers says.

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Nicotine Craving and Heavy Smoking May Contribute to Increased Use of Cocaine and Heroin

By Patrick Zickler, NIDA NOTES Staff Writer

People who abuse drugs are also likely to be cigarette smokers. More than two-thirds of drug abusers are regular tobacco smokers, a rate more than double that of the rest of the population. NIDA researchers have found that craving for nicotine appears to increase craving for illicit drugs among drug abusers who also smoke tobacco, and this relationship suggests that smokers in drug treatment programs may be less successful than nonsmokers in staying off drugs.

At NIDA's Intramural Research Program in Baltimore, Dr. Stephen Heishman and his colleagues examined the interaction of craving for nicotine and craving for other drugs and found that situations that increased desire to smoke also increased desire to use drugs. The study involved male and female adult smokers who were not trying to stop smoking and had histories of abusing alcohol, cocaine, heroin, marijuana, and/or other substances.

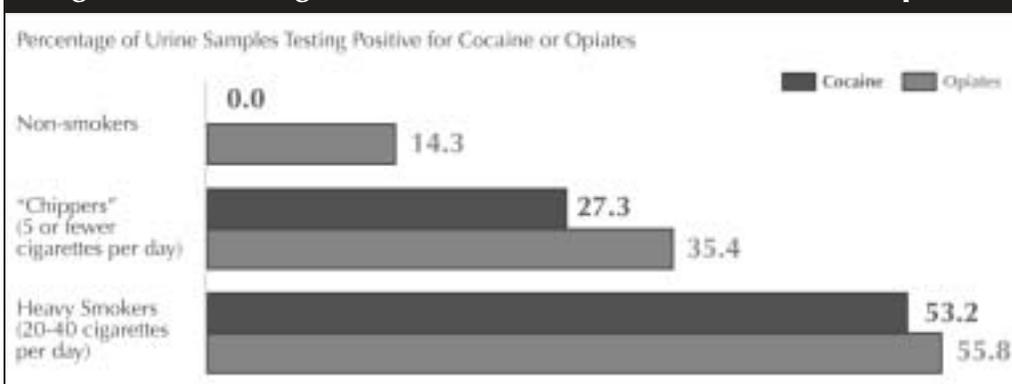
The researchers asked participants to listen to recorded scripts describing scenes and then to rate their urge to smoke and their desire to use other drugs. In the first part of the study, which involved 18 participants, the scripts had content that was generally pleasant (watching children on a sunny beach), unpleasant (a friend asking to borrow money), or neutral (doing household chores). Some scripts also included people expressing a desire to smoke, while others did not mention smoking at all (see "Cues Trigger Craving"). Both the scripts including a mention of smoking and those containing negative emotional content increased the participants' craving for drugs, as well as for smoking.

In the second part of the study, 24 participants heard scripts with only pleasant content (enjoying the beach, talking on the phone with an old acquaintance, or visiting friends). These scripts also contained descriptions of tobacco craving that increased in intensity from no mention of smoking to asking the question, "How could you really enjoy yourself fully unless you were smoking?" Participants reported that craving for both drugs and tobacco increased as the intensity of the tobacco craving messages in the scripts increased.

"One of our more interesting findings was that scripts that elicited craving for tobacco also elicited craving for the subject's drug of choice. This suggests that real-world situations that produce tobacco craving also may result in craving for drugs of abuse," Dr. Heishman says. The findings also suggest that treatment for heroin, cocaine, or alcohol addiction might be more effective if it included concurrent treatment of tobacco addiction, he says.

In a NIDA-supported study at the University of California, San Diego, doctoral candidate Dominick Frosch and his colleagues at the Integrated Substance Abuse Program at the University of California, Los Angeles, investigated the relationship between levels of cigarette smoking and levels of cocaine and heroin use among 32 individuals who had been in a methadone treatment program for at least 4 months. The participants included 10 nonsmokers (6 female, 4 male) and 22 smokers (16 female, 6 male). The smokers were equally divided among heavy smokers (20 to 40 cigarettes per day) and "chippers" who smoked 5 or fewer cigarettes per day.

Cigarette Smoking Associated With Use of Cocaine and Opiates



Among patients in a methadone treatment program for opiate addiction, levels of cocaine or opiate use were directly related to levels of cigarette smoking.

"Compared with heavy smokers, chippers have less intense craving for their first cigarette of the day and can more comfortably avoid smoking in situations where it is not permitted," Mr. Frosch explains.

The researchers evaluated the connection between tobacco smoking and illicit drug use among the smokers and non-smokers by using breath and urine samples from the participants over a 7-day period. They found that the amount of cocaine and heroin use was closely related to the level of tobacco use. "The more cigarettes smoked, the more likely the person was to use illegal drugs," Mr. Frosch says. "These findings provide compelling reasons for implementing smoking cessation programs for patients in methadone treatment, as the benefits of smoking cessation may extend to opiate addiction as well."

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Cues Trigger Craving

To evaluate the impact of the urge to smoke on craving for other drugs, Dr. Stephen Heishman and his colleagues asked participants to rate their desires for tobacco and other drugs after listening to recorded "scripts" of scenes involving pleasant, unpleasant, or neutral situations and containing "urge" or "no-urge" smoking cues. The scripts were originally developed by Dr. Stephen Tiffany and colleagues at Purdue University.

Pleasant, no-urge script: You're at the beach, lying on a blanket. The warm sun penetrates your skin and relaxes you thoroughly. A fresh breeze blows over your body as you run your hands through the clean white sand and let the grains fall through your fingers. You're feeling refreshed and at ease, and pleasant thoughts run through your mind. You can hear the sound of waves splashing rhythmically against the shore. Nearby there are some children playing a game. A bright red beach ball lands near your blanket. You look up and see two of the children running toward you to get their ball. You stand up, pick up the ball, and toss it to them. They laugh and giggle and run back to their game. You go to the blanket and lie down. You're enjoying this day completely.

Pleasant, urge script: You're at a friend's house sitting in a big comfortable chair. You're with people you've known a long time, and you're enjoying yourself very much. You're sipping a drink, and you're feeling totally at ease. Many of your friends are smoking cigarettes, just as you used to do. You've gone an entire week without smoking. As you sit there listening to the conversation and laughter, you begin to wonder what a cigarette would taste like. The more you think about smoking, the stronger your desire becomes. Maybe just tonight when you're with your friends and having a good time, it would be okay to smoke. How could you really enjoy yourself fully unless you were smoking? Your desire to smoke becomes intense, and you know that there's no good reason not to ask one of your friends for a cigarette.

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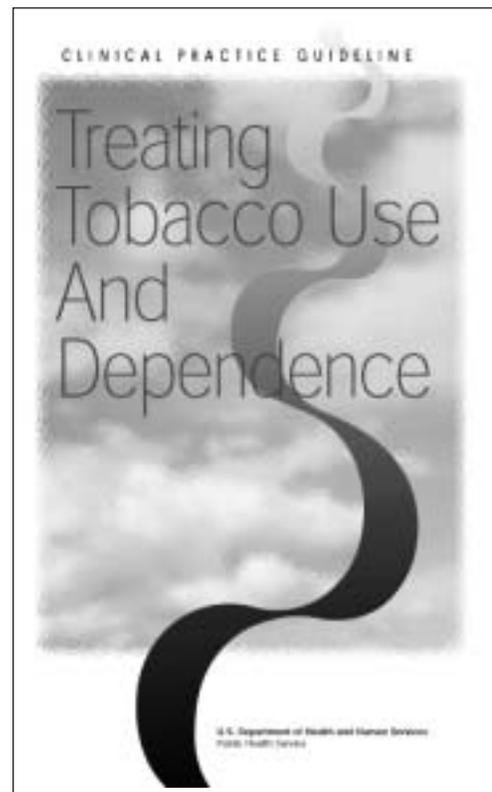
New Clinical Guidelines Describe Proven Treatments for Nicotine Addiction

By Patrick Zickler, *NIDA NOTES* Staff Writer

The U.S. Surgeon General, Dr. David Satcher, has released a new set of guidelines for primary care practitioners, "Treating Tobacco Use and Dependence: A Clinical Practice Guideline." The guidelines, released in June, are based on an evaluation of nearly 6,000 peer-reviewed research studies. They recommend pharmacotherapies such as nicotine replacement therapy by patch, gum, inhaler, and nasal spray, and sustained release bupropion, as well as behavioral therapy, counseling, and support programs to help patients overcome their addiction to nicotine.

NIDA—along with the National Cancer Institute; the Centers for Disease Control and Prevention; the National Heart, Lung, and Blood Institute; the Agency for Healthcare Research and Quality; The Robert Wood Johnson Foundation; and the University of Wisconsin Medical School's Center for Tobacco Research and Intervention—sponsored development of the guidelines.

Copies of "Treating Tobacco Use and Dependence: A Clinical Practice Guideline" and a consumer guide called "You Can Quit Smoking" are available by calling 1-800-358-9295 or writing to Publications Clearinghouse, P.O. Box 8547, Silver Spring, MD 20907-8547. The documents also are available at: www.surgeongeneral.gov/tobacco/default.htm. **NN**



Gender Differences in Drug Abuse Risks and Treatment

By Patrick Zickler, *NIDA NOTES* Staff Writer

Over the past few years NIDA has made a major research commitment to identifying and understanding differences in the ways that women and men—or girls and boys—are first exposed to drugs, in their risks of abuse and addiction, and in the effectiveness of drug treatment. Understanding these differences, and incorporating that understanding into drug abuse prevention and treatment, can reduce the dangers and improve outcomes. NIDA-supported research has shown that gender differences play a role from the very earliest opportunity to use drugs, that women and men tend to abuse different drugs, that the effects of drugs are different for women and men, and that some approaches to treatment are more successful for women than for men.

Are Women Less Likely Than Men to Abuse Drugs?

Men are more likely than women to have opportunities to use drugs, but men and women given an opportunity to use drugs for the first time are equally likely to do so and to progress from initial use to addiction. However, women and men appear to differ in their vulnerability to some drugs. Both are equally likely to become addicted to or dependent on cocaine, heroin, hallucinogens, tobacco, and inhalants. Women are more likely than men to become addicted to or dependent on sedatives and drugs designed to treat anxiety or sleeplessness, and less likely than men to abuse alcohol and marijuana. There are also differences between men and women who seek treatment for drug abuse. Women in treatment programs are less likely than men to have graduated from high school and to be employed and are more likely than men to have other health problems, to have sought previous drug treatment, to have attempted suicide, and to have suffered sexual abuse or other physical abuse.

Are There Gender Differences In the Biological Effects of Drugs?

Animal research and human studies have revealed that males and females may differ in their biological responses to drugs. In studies of animals given the opportunity to self-administer intravenous doses of cocaine or heroin, females began self-administration sooner than males and administered larger amounts of the drugs. Women may be more sensitive than men to the cardiovascular effects of

cocaine. In human studies, women and men given equal doses of cocaine experienced the same cardiovascular response despite the fact that blood concentrations of cocaine did not rise as high in women as in men. In studies involving long-term cocaine users, women and men showed similar impairment in tests of concentration, memory, and academic achievement following sustained abstinence, even though women in the study had substantially greater exposure to cocaine. Women cocaine users also were less likely than men to exhibit abnormalities of blood flow in the brain's frontal lobes. These findings suggest a sex-related mechanism that may protect women from some of the damage cocaine inflicts on the brain.

Does Gender Play a Role in Nicotine Addiction?

Women and men are equally likely to become addicted to nicotine, yet women typically smoke cigarettes with lower nicotine content than those smoked by men, smoke fewer cigarettes per day, and inhale less deeply than men. Overall, however, women are less successful than men in quitting smoking and have higher relapse rates after they do quit. Treatment involving nicotine replacement therapy—nicotine gum or patch—works better for men than for women.

What Are Women's Risks for HIV/AIDS?

Research suggests that there are sex-related differences in some fundamental aspects of the HIV/AIDS disease process. For example, an HIV-infected woman with half the amount of virus circulating in the bloodstream as an infected man will progress to a diagnosis of AIDS in about the same time. And, according to the Centers for Disease Control and Prevention, among cases that progress to a diagnosis of AIDS, drug abuse accounts for a greater percentage of cases among women than among men. Nearly half (47 percent) of all women diagnosed with AIDS are injecting drug users (IDUs), whereas among men, IDUs account for 32 percent of AIDS cases. An additional 19 percent of women, compared with 2 percent of men, with AIDS report having sex with users who inject drugs. In all, drug abuse is nearly twice as likely to be directly or indirectly associated with AIDS in women (66 percent) as in men (34 percent).

For More Information

NIDA's gender-related research is discussed in Drug Addiction Research and the Health of Women, available on NIDA's home page on the World Wide Web:

www.drugabuse.gov or from the National Clearinghouse for Alcohol and Drug Information (NCADI), P.O. Box 2345, Rockville, MD 20847-2345, (800) 729-6686. 

Evidence Builds That Genes Influence Cigarette Smoking

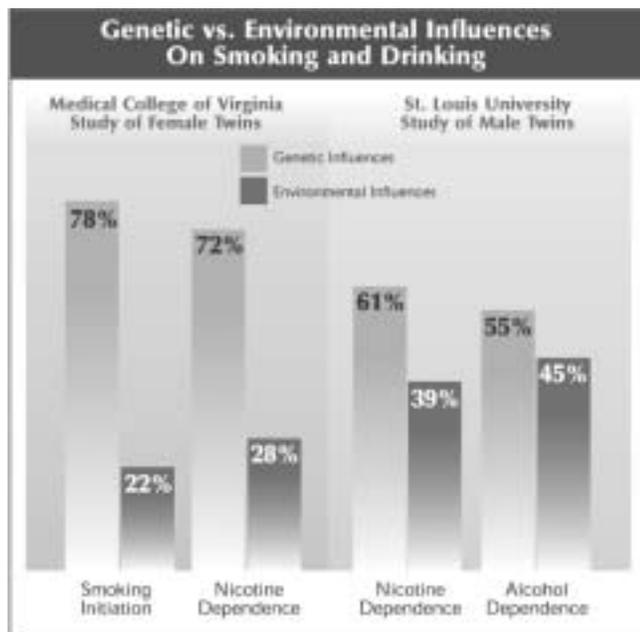
By Patrick Zickler, NIDA NOTES Staff Writer

More than one in four Americans older than 17 regularly smokes cigarettes despite increasing public awareness of tobacco's severe health risks. Some start younger than others and, among those who try to quit, some are more successful than others. NIDA-supported scientists are finding increasing evidence that these differences may be due in part to an inherited vulnerability to nicotine addiction.

At the St. Louis University Health Sciences Center, Dr. William True and Dr. Hong Xian interviewed male twin pairs to assess genetic influences on smoking. In twin studies, researchers compare patterns of tobacco use in fraternal and identical twin pairs, who typically are exposed to common environmental influences. If genes play a role in determining tobacco use, identical

twins—who share the same genes—will be more similar in their use of tobacco than fraternal twins, who share roughly half of their genes. The St. Louis University researchers found that among the 3,356 twin pairs studied, genetic factors make a stronger contribution to nicotine dependence (61 percent) than do environmental factors (39 percent) and also play a more prominent role (55 percent) than environmental factors (45 percent) in alcohol dependence. In another study, Dr. Kenneth Kendler and his colleagues at the Medical College of Virginia in Richmond interviewed 949 female twin pairs and found that genetic factors play a more important role (78 percent) than do environmental factors (22 percent) in smoking initiation and in nicotine dependence (72 percent vs. 28 percent).

"These studies emphasize the importance of understanding the role of genetic influences in smoking," says Dr. Jaylan Turkkan, chief of NIDA's Behavioral Sciences



A Medical College of Virginia study involving 949 female twin pairs found genetic factors to be more influential than environmental factors in smoking initiation and nicotine dependence. Likewise, a St. Louis University study of 3,356 male twin pairs found genetic factors to be more influential for dependence on nicotine and alcohol.

Research Branch. "The more we understand about vulnerabilities, risks, and possible protective factors, the better able we will be to tailor treatments that help people stop smoking."

Other NIDA-supported scientists are studying genes that are polymorphic—that is, in different individuals the same gene has slight variations called alleles—and have found that individuals with one type of allele are more likely to begin smoking or to have greater success quitting than are individuals with another type. For example, researchers at the University of Toronto have found that different alleles in a gene that helps regulate nicotine metabolism may protect some smokers from becoming dependent on nicotine (see "Study Shows How Genes Can Help Protect from Addiction," V13-6, 1998).

Dr. Caryn Lerman, principal investigator of the NIDA-supported Transdisciplinary Tobacco Use Research Center at Georgetown University in Washington, D.C., and her colleagues studied two genes, designated SLC6A3 and DRD2, that may influence smoking behavior by affecting the action of the brain chemical dopamine. In a study involving 289 smokers and 233 nonsmokers (42 percent male, 58 percent female, average age 43), the researchers found that smokers were less likely to have an allele designated SLC6A3-9 (46.7 percent) than were nonsmokers (55.8 percent). The likelihood of smoking was even lower if the individual had both the SLC6A3-9 allele and the DRD2-A2 allele. In addition, Dr. Lerman observed that smokers with the SLC6A3-9 allele were more likely to have started smoking later and to have had longer periods of smoking cessation than those without the allele. These findings imply that the allele may impart a protective

effect. Therefore, Dr. Lerman suggests, smokers without the SLC6A3-9 allele may be better able to quit smoking if their treatment incorporates a medication such as bupropion that acts on the brain's dopamine pathway. This hypothesis is currently being tested in a randomized trial.

Dr. Lerman and her colleagues also studied a polymorphism in a gene, designated 5-HTTLPR, that helps regulate the brain chemical serotonin to determine the gene's possible role in smoking. The polymorphism has two alleles, one designated the short, or S, allele, the other the long, or L allele. In previous studies the S allele has been linked to neuroticism—an anxiety-related personality trait. Dr. Lerman and her colleagues studied 185 smokers (46 percent male, 54 percent female, and average age 45) to investigate the possible relationship between genetically influenced neuroticism and smoking behavior. They found that neuroticism was associated with increased nicotine dependence, smoking for stimulation, and smoking to relieve negative mood in the group of smokers who had the S allele. Among smokers with the L allele, neuroticism was not associated with these smoking patterns. "Anxious persons tend to smoke more and have more difficulty quitting," Dr. Lerman says. The new findings suggest that among smokers with neuroticism, determining the 5-HTTLPR genotype may help identify who will be more responsive to a particular type of treatment. "Once validated, these results may lead to targeted pharmacotherapy

"The more we understand about vulnerabilities, risks, and protective factors, the better able we will be to help people stop smoking."

for smoking cessation," says Dr. Lerman.

"This area of research represents our first small steps along a very complicated path to understanding the role that genes play in drug abuse," notes Dr. Harold Gordon of

NIDA's Clinical Neurobiology Branch. "Many genes interact with each other and with other biological and environmental factors. Defining these interactions and understanding their influence on nicotine addiction will be crucial to development of treatments for smoking and for other addictions."

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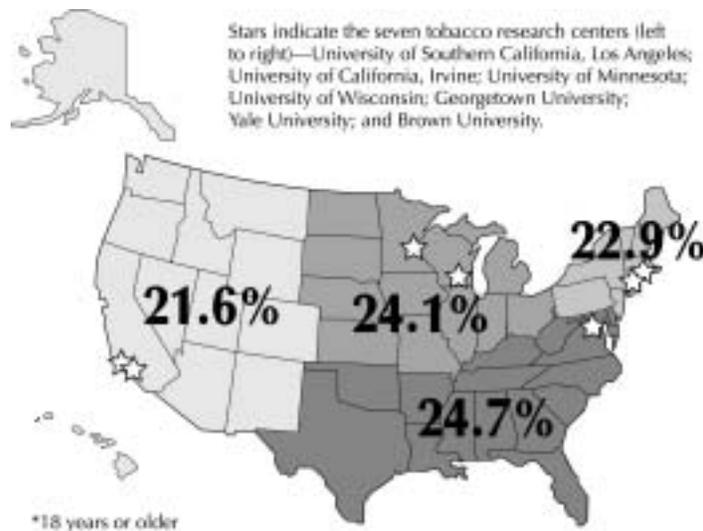
NIDA Joins NCI, Robert Wood Johnson Foundation To Launch Tobacco Research Centers

By Patrick Zickler, NIDA NOTES Staff Writer

NIDA, the National Cancer Institute (NCI), and The Robert Wood Johnson Foundation (RWJF) have awarded grants to seven academic research institutions to establish Transdisciplinary Tobacco Use Research Centers (TTURCs) devoted to investigating new ways to combat tobacco use and nicotine addiction. The institutions will receive \$70 million from NIDA and NCI for the project. RWJF will provide an additional \$14 million over 5 years to support improved communications and policy development at the TTURCs.

In the past, research grants typically have focused on single components of tobacco use and nicotine addiction, treatment, or prevention, notes Dr. Jaylan Turkkan, chief of NIDA's Behavioral Sciences Research Branch and coordinator of NIDA's TTURC efforts. "The transdisciplinary approach will bring together collaborators who will have the freedom to investigate wider aspects of nicotine addiction, such as factors that influence smoking initiation, and to study the issues at levels ranging from genetics to peer interactions," Dr. Turkkan says.

"The transdisciplinary centers represent an important new approach to research," says NIDA Director Dr. Alan I. Leshner. "Tobacco use and nicotine addiction are incredibly complex subjects, and transdisciplinary investigation can give us the broad perspective we need to understand the etiology of this addiction. This approach will lead to the development of new interventions that will help prevent tobacco use, particularly among teens and younger children."



Although the prevalence of adult cigarette smokers is high, the numbers reflect only one piece of the problem. NIDA's new research centers will seek ways to combat all types of tobacco use among all population segments, adults and children alike. Statistics from Centers for Disease Control and Prevention in Atlanta.

The TTURC concept evolved from informal conversations among researchers and policymakers at a July 1998 conference—"Addicted to Nicotine"—cosponsored by NIDA, RWJF, NCI, and the Centers for Disease Control and Prevention. Several months later, NCI's Tobacco Research Implementation Group recommended transdisciplinary centers as its highest tobacco use research priority. Within a year, NIDA and NCI jointly issued a Request for Applications from academic centers interested in developing such centers. The first TTURC awards were announced in October 1999. The centers, principal investigators, and research areas are:

- Brown University Center for Behavioral and Preventive Medicine at the Miriam Hospital, Providence, Rhode Island; Principal Investigator Dr. David Abrams; Research Area Identification of early childhood and lifetime psychiatric factors that determine smoking initiation, dependence, use patterns, cessation, and response to cessation treatment.
- University of California, Irvine; Principal Investigator Dr. Frances Leslie; Research Area Identification of predictors of nicotine addiction in animals and tobacco susceptibility and use in humans;
- University of Southern California, Los Angeles; Principal Investigator Dr. C. Anderson Johnson; Research Area Preventing tobacco use among youth of diverse cultures.

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- Georgetown University, Washington, D.C.; Principal Investigator Dr. Caryn Lerman; Research Area Identification of biobehavioral basis of smoking initiation, smoking treatment, and harm from tobacco exposure.
 - University of Minnesota, Minneapolis; Principal Investigator Dr. Dorothy Hatsukami; Research Area Treating smokers who have been resistant to conventional methods of intervention or who have not been previously targeted.
 - University of Wisconsin Medical School, Madison; Principal Investigator Dr. Michael Fiore; Research Area Relapse to tobacco use.
 - Yale University, New Haven, Connecticut; Principal Investigator; Dr. Stephanie O'Malley; Research Area Treatment of tobacco addiction. 

Nicotine Medication Also Reduces Craving in Cocaine Addicts

By Patrick Zickler, *NIDA NOTES* Staff Writer

Craving, the almost irresistible urge to use drugs, is one of the most vexing problems associated with drug addiction.

Craving is the result of changes that drugs cause in the brain and may be triggered by physical discomfort associated with abstinence from the drug.

Craving also may be triggered by external, environmental factors, such as the sights, sounds, and social situations associated with drug use. In this "cue-induced" craving, the urge to use drugs often is powerful enough to cause a relapse to drug abuse months or even years after a person has stopped using drugs.

Dr. Malcolm Reid, a NIDA-supported researcher at the New York University School of Medicine and the New York Veterans Affairs Medical Center in New York City, has found that mecamylamine—a medication that blocks the rewarding effects of nicotine—can reduce cue-induced craving in patients addicted to cocaine and may help these patients avoid relapse.

In earlier research, Dr. Reid found that nicotine significantly increased cue-induced craving for cocaine in addicted patients who also smoked tobacco. "This finding suggested that a medication like mecamylamine, which blocks some of nicotine's effects in the brain, might also reduce the cue-induced craving that nicotine causes," Dr. Reid says.

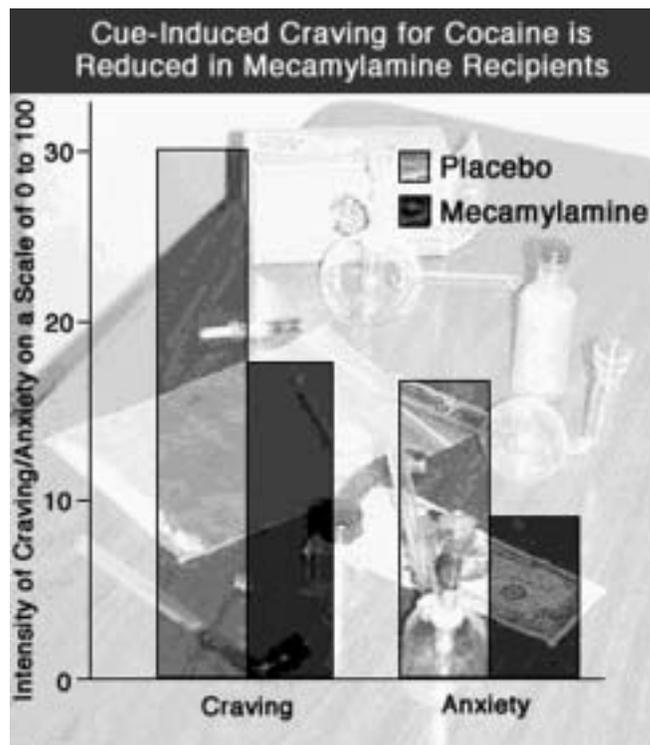
Dr. Reid recruited 23 cocaine-addicted patients, 20 men and 3 women with an average age of 40, from outpatient drug addiction treatment programs. All patients were regular cigarette smokers and had used crack cocaine within the last 3 months. Patients were instructed to abstain from tobacco for at least 1 day and from cocaine for 2 days before participating in the craving test sessions. Abstinence was verified by laboratory tests.

The participants were shown a series of neutral cues as well as cocaine-related cues. During each test session, participants first viewed the neutral cues, including videotaped images of pine cones and seashells, and then handled rocks, pine cones, and seashells and smelled a fragrant spice. Participants then completed a survey that asked them to describe their mood—for example, "anxious," "nervous," or "irritated"—and rate the intensity

"Those who received mecamylamine reported significantly less intense cocaine craving—only half as strong on average."

of their desire to use cocaine and the likelihood that they would use cocaine if it were available. Following exposure to neutral cues, participants were randomly given either mecamylamine or placebo. Two hours later they were

exposed to a series of cocaine-related cues, which included videotaped scenes in which actors simulated purchasing and smoking crack cocaine and scenes of actual crack smoking. The participants then handled drug paraphernalia and a substance that looked like crack cocaine, and smelled a crack pipe that had been treated with an artificial residue with the same aroma as



Twenty-three patients were asked to rate the intensity (on a scale ranging from 0 to 100) of their craving for cocaine and their feeling of anxiety after viewing and handling cocaine-related objects like those shown in the background of the graph. Patients who received mecamylamine before exposure to the objects reported significantly less anxiety and craving for the drug.

crack cocaine. As before, they rated their mood and desire to use cocaine. The procedure was repeated 2 to 3 days later, with patients who had received mecamylamine during the first session receiving placebo during the second session, and vice versa.

"All the patients reported that they felt an increased craving for cocaine after the cocaine-related cue sessions, but those who received mecamylamine reported less anxiety and significantly less intense cocaine craving—only half as strong on average—than did the patients who received placebo," Dr. Reid says. "In addition, the patients who received the medication reported less intense symptoms of tobacco withdrawal prior to being exposed to cocaine-related cues."

The success of mecamylamine in reducing both cue-induced craving for cocaine and the rewarding effects of nicotine has important implications in treatment. Epidemiologic studies show that smoking is more prevalent among cocaine-addicted persons than in the general population and that cocaine-addicted smokers begin using cocaine at an earlier age and use it more frequently than cocaine-addicted nonsmokers. "In earlier studies we found that nicotine may intensify cue-induced craving for cocaine, which can make it difficult for cocaine addicts to stop using the drug. We now know that mecamylamine

may reduce cue-induced cocaine craving and it does so even when subjects do not have nicotine in their system," Dr. Reid says.

"Previous clinical and preclinical studies have suggested that mecamylamine has therapeutic potential in the treatment of smoking cessation and alcoholism," Dr. Reid notes. "Our current findings indicate it could also play an important role in reducing the risk of relapse for patients in treatment for cocaine addiction." To further investigate this possibility, Dr. Reid is now conducting a clinical trial of mecamylamine treatment of cocaine addiction at the New York Veterans Affairs Medical Center.

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Teen Alternative to Cigarettes Has Higher Concentrations of Nicotine

Although hand-rolled cigarettes from India, called bidis (pronounced "beedees"), are an increasingly popular alternative to conventional cigarettes among teens in the United States, they are not a less addictive option, a NIDA study has confirmed. Dr. Wallace B. Pickworth and his colleagues in NIDA's Intramural Research Program in Baltimore and at Murty Pharmaceuticals in Lexington, Kentucky, compared a dozen brands of bidis with a brand

of U.S. commercial unfiltered cigarettes and found that 11 of the 12 bidi brands had 28 percent higher nicotine concentrations than the unfiltered cigarettes. In the United States, bidis are sold in tobacco shops and other outlets and come in colorful packages with flavor choices such as cinnamon, orange, and chocolate. In India, where bidis have been smoked for centuries, they are not flavored. **NN**

New NIDA Clinic Tests Therapies to Help Teens Quit Smoking

By Steven Stocker, *NIDA NOTES* Contributing Writer

NIDA's Intramural Research Program (IRP) recently opened a new Teen Tobacco Addiction Treatment Research Clinic at the Bayview Medical Center in Baltimore. At the clinic, researchers will evaluate promising therapies for adolescent nicotine addiction.

One of the clinic's first research projects will be a pilot study of smoking cessation treatments for 13- to 17-year-old cigarette smokers. "More than one-third of 17-year-olds who smoke say they are interested in some form of treatment to help them quit," says IRP's Dr. Eric Moolchan, director of the new clinic and leader of the smoking cessation study.

The research project will test the combination of nicotine replacement therapy (NRT) and group counseling for treating nicotine addiction in adolescents. NRT helps smokers learn to abstain from smoking by replacing the nicotine that they previously obtained from cigarettes, thereby preventing withdrawal symptoms and craving for nicotine. NRT forms currently available include the nicotine patch and gum.

Dr. Moolchan says that many health care providers are reluctant to prescribe nicotine patches or gum for adolescents because of a lack of studies showing that these products are safe and effective in this age group. The IRP pilot study will help determine whether adolescents can use the nicotine patch and gum safely, whether they can tolerate the same nicotine doses in the patch and gum as adults, and whether they will follow the instructions on how to use these products. Later studies will focus more on the effectiveness of the patch and gum in helping adolescents quit smoking.

"It's important that we develop effective treatments for young people to try to get them to quit smoking as early as possible," says IRP Director Dr. Barry Hoffer.

"Research shows that 90 percent of people who die



Cutting the ribbon to dedicate NIDA's new Teen Tobacco Addiction Treatment Research Clinic (TTATRC) in Baltimore are, from left, Dr. Jean Lud Cadet, clinical director, NIDA's Intramural Research Program (IRP); NIDA Director Dr. Alan I. Leshner; Dr. Barry Hoffer, director of NIDA's IRP; Dr. Eric Moolchan, director of TTATRC; and Dr. Monique Ernst, IRP researcher.

prematurely of a cigarette-related disease started smoking when they were adolescents. If we can help adolescents quit smoking, we should be able to prevent many of these premature deaths."

The IRP study will have 3 groups, each with 18 adolescents. The first group will receive active patches containing nicotine and placebo gum without nicotine, the second group will receive placebo patches and active gum, and the third group will receive placebo patches and placebo gum. Participants will not be told whether the products they receive are active or placebo.

All three groups will also participate in group counseling sessions because studies with adult smokers have indicated that smoking cessation programs that combine behavioral therapy with medications produce the highest abstinence rates. In the counseling sessions, a mental health professional and Dr. Moolchan, who is a pediatrician, will discuss various topics involving smoking and health and will teach the adolescents how to modify their behavior to deal with situations that might cause them to smoke.

Even though smoking is the primary focus of the sessions, other topics—such as peer relations, school, and dating—will be discussed. "Addressing these other issues is important because adolescent smokers often think that smoking helps them in their social relations," says Dr. Moolchan. "Furthermore, problems concerning social relations can negatively affect mood, and smokers often regulate their mood with nicotine."

The IRP project also will examine other aspects of adolescent smoking. One study will analyze how adolescents smoke cigarettes—for example, how deeply they inhale or how many puffs they take per cigarette. IRP researchers

will also study whether nicotine withdrawal causes adolescents to experience problems with concentration and short-term memory and whether nicotine-replacement treatments can reverse these deficits. Another project will measure chemical evidence of cigarette consumption in saliva to determine whether adolescents metabolize the components of

“More than one-third of 17-year-olds who smoke say they are interested in some form of treatment to help them quit.”

cigarette smoke in the same way that adults do.

The researchers will recruit adolescents from the Baltimore area through referrals from healthcare providers, schools, churches, and youth centers. Dr. Moolchan hopes that this study will establish contacts in the community that can be used to recruit adolescents for future studies. **NN**

New Tracers Will Help Researchers Track Nicotine in the Brain

Dr. Edythe D. London and her colleagues at the Brain Imaging Center of NIDA's Intramural Research Program in Baltimore have developed a new class of radio-labeled chemicals capable of binding tightly to nicotinic acetylcholine receptors, the molecules in the brain where nicotine acts. These probes will enable scientists to monitor nicotinic pathways in the brain by external imaging. Because these radiotracers attach themselves with more selectivity and less toxicity than currently available nicotinic radiotracers, researchers believe they may be ideal for both positron emission tomography (PET) and single photon emission computed tomography (SPECT), two common brain imaging technologies.

Testing in primates has led scientists to conclude that this new class of radiotracers will be practical for studying the underlying mechanisms of nicotine dependence in humans and will be useful for developing and testing therapies for nicotine addiction. These radiotracers may also benefit the study of Alzheimer's disease, Parkinson's disease, and Tourette's syndrome, which scientists believe are conditions characterized at least in part by abnormalities in nicotinic receptors. The Brain Imaging Center is now seeking FDA approval to use the new radiotracers in studies with human volunteers. **NN**

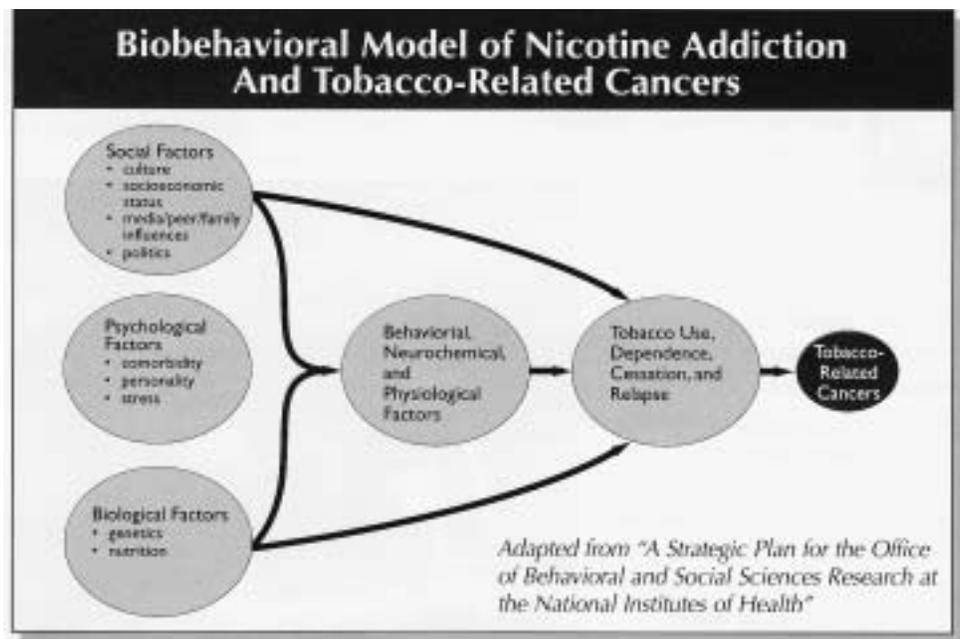
NIDA Teams With National Cancer Institute to Establish Tobacco Research Centers

By Robert Mathias, NIDA NOTES Staff Writer

NIDA is joining with the National Cancer Institute (NCI) to create tobacco research centers across the Nation. The centers will bring together scientists in areas as diverse as molecular biology and social marketing to collaborate on research to reverse the tide of tobacco-related diseases that claims more than 430,000 lives in the U.S. each year. NIDA will commit at least \$20 million and NCI will commit \$50 million over the next 5 years to fund the centers, which will augment ongoing tobacco research by both Institutes. The Institutes expect to fund at least five centers this year.

The joint NCI/NIDA initiative is soliciting research proposals from investigators across the country to establish Transdisciplinary Tobacco Use Research Centers to study the prevention of tobacco use, initiation of tobacco use, addiction to tobacco, and/or treatment of tobacco addiction and tobacco-related cancers. Each center also will focus on different areas in which there are gaps in knowledge, such as adolescent smoking and the use of tobacco products besides cigarettes, such as cigars and spit tobacco. The overriding goal of the centers will be to support innovative transdisciplinary research that is likely to have the greatest impact on reducing tobacco use and its consequences around the world.

"The collaboration between NCI and NIDA emphasizes the need to focus on all aspects of the tobacco problem—the causes, prevention, and treatment of nicotine addiction and the dramatic health consequences of tobacco use," says NIDA Director Dr. Alan I. Leshner. "By taking a comprehensive approach to the problem, these centers will accelerate the development of broadly effective tobacco use prevention and treatment interventions."



The tobacco research centers will bring together scientists to collaborate on research that addresses the many factors, such as those shown here, that may lead to nicotine addiction and cancer.

The initiative to create tobacco research centers comes in the face of an increase in cigarette smoking by young people in recent years as charted by NIDA's annual Monitoring the Future surveys of drug use among high school and college students. In addition, data from the Centers for Disease Control and Prevention in Atlanta indicate that, after decades of decline, rates of tobacco use by adults have stabilized at about 26 percent of the U.S. population.

The new tobacco research centers will address pressing unresolved issues that underlie these trends in tobacco use, such as: Why do some children who experiment with tobacco become addicted, while others do not? How can people be helped to quit smoking? Are there genes that predispose some people to tobacco addiction or protect them from it? Because the answers to such questions lie hidden in a web of complex genetic, social, cultural, and economic factors, the centers will study tobacco use in ways that will integrate biological and psychosocial models of tobacco use and addiction. The centers will foster

"We seem to be in the middle of a turnaround in young people's use of most kinds of illicit drugs following an earlier period of sustained increases."

collaborative research among scientists with expertise in areas that include molecular biology, genetics, neuroscience, epidemiology, imaging, primary care, behavioral science, communications, health policy, economics, and marketing.

For More Information

Additional information about the tobacco research centers can be obtained through NIDA's home page on the World Wide Web at <http://www.nida.nih.gov/> by clicking on Transdisciplinary Tobacco Use Research Centers. The site, which includes contact names, the request for applications, and a list of additional resources, will be updated periodically. **NN**

Studying the Long-term Consequences of Prenatal Exposure to Marijuana and Cigarettes

For more than 15 years, Dr. Peter A. Fried, professor of psychology at Carleton University in Ottawa, Canada, has studied mother-child pairs to determine whether prenatal exposure to marijuana, cigarettes, or both affects the development and behavior of children and adolescents. Dr. Fried's MERIT Award will allow him to continue to follow the mother-child pairs as the children develop through their teenage years.

"Dr. Fried's research represents an immense opportunity to obtain previously unattainable information on the long-term consequences of prenatal exposure to marijuana and cigarettes," says Dr. Vincent Smeriglio of NIDA's Center for AIDS and Other Medical Consequences of Drug Abuse. "His research already has made a significant contribution not only to documenting infancy and childhood consequences, but also to exploring possible mechanisms for those consequences."

Dr. Fried's research involves more than 150 children born in the Ottawa area who were exposed before birth to cigarettes, marijuana, or both. Dr. Fried and his colleagues evaluated the children several hours after birth and at 4 days, 7 days, 9 days, 30 days, 6 months, and 1 year. The researchers have evaluated the children annually since their first year to look for developmental and behavioral problems that might be related to prenatal exposure to marijuana or cigarettes. The researchers' findings suggest that marijuana exposure is associated with impaired executive functioning - the ability to make decisions and plan for the future - in the children at 9 to 12 years of age. "The major finding in this study about regular marijuana use during pregnancy is that marijuana can have an impact

that may prevent a child from achieving his or her full potential," Dr. Fried says.

Children born to women who smoked cigarettes during pregnancy showed, from infancy through early adolescence, a reduction in auditory-based abilities. From ages 9 to 12, children who were exposed prenatally to tobacco smoke showed a reduction in language scores and poorer performance in tests involving the auditory aspects of reading compared with children born to non-smokers, with the most heavily exposed children performing worse than those exposed to smaller amounts. "The continuity, over approximately 12 years, of the relationship between auditory and language variables and prenatal exposure to cigarette smoke suggests that these important aspects of behavior are directly affected by maternal smoking," Dr. Fried says.

The MERIT Award will simplify the continuation of this research through a crucial period of the children's development, Dr. Fried notes. "Testing the children at midadolescence is particularly critical. Subtle learning difficulties are most likely to manifest themselves at this stage of development, which involves complex behaviors requiring focused attention and cognitive skills," he says. **NN**



Dr. Peter A. Fried

Nicotine Conference Highlights Research Accomplishments And Challenges

By Barbara Cire, NIDA NOTES Associate Editor

Provocative new research findings about the nicotine addiction process, how nicotine addiction drives tobacco use, and nicotine addiction treatment were the focus of "Addicted to Nicotine: A National Research Forum," held in Bethesda, Maryland in July. The meeting was sponsored by NIDA and The Robert Wood Johnson Foundation and cosponsored by the National Cancer Institute and the Office on Smoking and Health of the Centers for Disease Control and Prevention. NIDA Associate Director Dr. Timothy P. Condon and Dr. Jaylan Turkkan, Chief of NIDA's Behavioral Sciences Research Branch, served as cochairs of the conference planning committee.

Keynote speaker Vice President Al Gore noted that the conference had drawn some of the world's best researchers "to reinforce that nicotine is a drug—a dangerous, highly addictive drug, and we should treat it as a drug." He cited recent research findings indicating that while the overall incidence of smoking has decreased, the number of adolescents starting to smoke has increased. "If children don't start smoking by age 19, they are unlikely to start," he said. "But, if they do start, it's hard to stop. Seventy percent of current smokers say they want to stop smoking, but can't. That's because nicotine is a highly addictive drug—as addictive as heroin or cocaine."

"We are here to apply the power of science to this problem," said NIDA Director Dr. Alan I. Leshner. He challenged the approximately 600 participants to highlight what is known about nicotine addiction and tobacco use and to "tell us what else we need to know to set the research agenda for the next decade." More than 40 scientists from the United States, Canada, and Sweden presented research results in four topic areas: the pharmacology of nicotine; individual and environmental risk factors for smoking initiation and nicotine intake; the biology of nicotine addiction; and treatment of nicotine addiction.

Dr. Jack Henningfield of The Johns Hopkins University School of Medicine in Baltimore said that, since the beginning of the 20th century, scientists have known that nicotine is a potent substance that affects the nervous system and stimulates heart rate and muscular activity, that nicotine's effects depend on the amount administered, and that responsiveness to nicotine diminishes with repeated use. NIDA-supported research has demonstrated conclusively that nicotine meets all the criteria of an addictive drug, he stressed.



In his keynote address at NIDA's nicotine conference, Vice President Al Gore tells participants that 3,000 young people start smoking each day, ultimately resulting in death for one-third of them.

Nicotine is now understood to affect the structure and function of the nervous system, Dr. Henningfield said.

Chronic nicotine exposure and withdrawal produce changes in brain function, including cerebral metabolism and hormone levels, he added.

Dr. Rachel Tyndale of the University of Toronto presented information about a gene variant for an enzyme called CYP2A6 that may protect some individuals from becoming addicted to nicotine. In humans, 60 to 80 percent of nicotine is metabolized by the CYP2A6 enzyme. Individuals with a defective version of the gene for CYP2A6 metabolize nicotine slowly and inefficiently. When people start to smoke, they often experience dizziness or nausea; when nicotine metabolism is slowed, these unpleasant effects may last longer, Dr. Tyndale explained. Thus, people with a defective version of this gene are less likely to continue smoking and, if they do smoke, are more likely to smoke less than people with a fully functioning version of this gene.

"This genetic defect protects approximately 7 million North Americans from smoking," said Dr. Tyndale. "Inhibiting the CYP2A6 enzyme may provide new therapeutic approaches to the prevention and treatment of smoking. The manipulation of CYP2A6 must be explored."

Dr. Marina Picciotto of Yale Medical School in New Haven, Connecticut, discussed a particular protein that she and her colleagues in France, Sweden, and Switzerland have identified as essential to the nicotine addiction process. Using sophisticated bioengineering tools, the researchers produced a strain of mice that lack this protein. They found that the genetically altered mice did not experience the normal rewarding and reinforcing aspects of nicotine that typically lead to addiction.

"The majority of smokers try to quit on their own without seeking help. The quit rate for this group is 5 percent or less," said Dr. Maxine Stitzer of The Johns Hopkins University School of Medicine, summarizing treatment research that compared the effectiveness of nicotine replacement therapy and behavioral therapy separately and combined. Because these treatments operate by different mechanisms, complementary and potentially additive effects may be expected when they are used in combination, she said.

"Typical long-term abstinence rates of 6 to 12 months for one type of therapy alone are about 20 percent," Dr. Stitzer said. "Combining therapies can produce long-term abstinence rates as high as 35 to 40 percent. We need to know how to improve access, affordability, and acceptability of both pharmacologic and behavioral therapies to take



Dr. Marina Picciotto of Yale Medical School discusses a recently identified protein that is involved in the reinforcing and rewarding aspects of nicotine addiction.

better advantage of existing treatments such as over-the-counter nicotine-replacement products. We must also learn how to strengthen the linkage between the two therapy types."

For More Information

Additional information about nicotine and its addictive properties can be obtained by calling NIDA Infofax at 1-888-NIH-NIDA (644-6432) or by accessing NIDA's home page on the World Wide Web at www.nida.nih.gov and going to the Addicted to Nicotine conference information. **NN**

New Publications Disseminate Research Findings on Nicotine

Two new publications that provide research-based information on nicotine addiction were released at NIDA's Addicted to Nicotine Conference in July.

"Nicotine Addiction," an eight-page report, provides the latest information about nicotine and its addictive properties, including:

- how nicotine in tobacco smoke and chewing tobacco affects the body;
- how nicotine tolerance develops over time;
- the medical consequences of nicotine use;
- gender differences in nicotine sensitivity; and
- the risks of smoking during pregnancy.



Current treatments for nicotine addiction, including nicotine replacements, behavioral therapies, and a new non-nicotine prescription drug, also are discussed. A glossary and list of resources for further information are included. "Nicotine Addiction" is part of the NIDA *Research Report* series. "The Brain's Response to Nicotine" is a new addition to NIDA's award-winning *Mind Over*

Matter magazine series. The series is designed to teach students in grades 5 through 9 how specific drugs affect the brain. The full-color minimagazine on nicotine describes



NIDA Director Dr. Alan I. Leshner presents the new NIDA publication, "Nicotine Addiction," to conference participants.

how tobacco smoke delivers nicotine to the brain, how nicotine disrupts brain function, and why it is so difficult for people to stop smoking. The magazine unfolds into an 11-by-23-inch poster displaying an image of the nerve cells involved in pain and touch.

Both publications can be downloaded from NIDA's home page on the World Wide Web at www.nida.nih.gov. Copies are available from the National Clearinghouse on Alcohol and Drug Information, P.O. Box 2345, Rockville, MD 20847-2345, (800) 729-6686 or (301) 468-2600, TDD number: (800) 487-4889, fax: (301) 468-6433, e-mail: info@health.org. **NN**

Addiction Research Can Provide Scientific Solutions to the Problem of Cigarette Smoking

By NIDA Director Dr. Alan I. Leshner

Every year, tobacco-related illnesses take the lives of more than 430,000 Americans. The force behind this grim statistic is the chronic, relapsing brain disease of addiction—in this case, addiction to nicotine. Only research on nicotine addiction can provide effective, science-based solutions to this costly public health problem.

More than two decades of NIDA leadership in addiction research have already provided much scientific information about addiction to nicotine. This research has led to the development of smoking prevention and treatment approaches that are helping to counter nicotine's threat to the public health today. NIDA-supported basic and clinical research promises additional improvements in treatment as scientists continue to unravel the mysteries of addiction to nicotine and other abused drugs.

Most smokers know that cigarette smoking and other forms of tobacco use are harmful. Nearly 35 million of them try to quit every year. Yet, without help, only a very small number actually are able to succeed. Science has shown why this is so. The nicotine in tobacco products is a highly addictive drug, and nicotine addiction is characterized by truly compulsive seeking and use, even in the face of harmful consequences.

Research on nicotine addiction has yielded a variety of pharmacological and behavioral treatments that have helped many people combat their nicotine addiction. For example, NIDA-supported research facilitated the development of nicotine replacement therapies, such as nicotine chewing gum and the transdermal nicotine patch, that enable many people to stop smoking. Yet, both research and extensive clinical experience have taught us that treating addiction with medication alone is not nearly as effective as when we couple the medication with a behavioral treatment. For example, we know that less than 10 percent of the people who try to quit smoking on their own are able to refrain from smoking for a year.



Research on nicotine addiction has yielded a variety of treatments that have helped many people combat their nicotine addiction.

Pharmacological treatments such as the patch and gum can double the odds of success. However, a combination of pharmacological treatment and behavioral treatment, such as group therapy or social support networks, can improve a smoker's chance of quitting even more.

NIDA's extensive behavioral research program is striving to increase the behavioral treatment options that clinicians can use with pharmacological treatments. Studies now under way are developing new, individualized behavioral treatments that will better

motivate smokers to stop smoking and teach them techniques that will enable them to remain abstinent. Other treatment studies are testing whether currently available behavioral therapies, such as contingency management and relapse prevention, are more effective used alone or in combination to help smokers quit.

While we have made much progress in developing treatments for nicotine addiction, we can and must do more to help the many smokers who still are unable to quit smoking. I am happy to report that ongoing research by NIDA-supported scientists has been uncovering important new information about the nicotine addictive process and how that process drives smoking behavior. We can use these data to help us develop new treatments.

Two recent studies have confirmed inferences from earlier research that some of nicotine's most important effects on emotions and behavior are exerted through the same brain circuits that are activated by other abused drugs. One study shows that, like other drugs of abuse, nicotine elevates levels of the neurotransmitter dopamine in brain pathways that control reward and pleasure. This change in dopamine levels is thought to be a fundamental characteristic of all addictions. The second study shows that, as with withdrawal from other addictive drugs, withdrawal from chronic nicotine use decreases this brain circuit's sensitivity to pleasurable stimulation. Our increased

understanding of these changes shows us why it is so hard for people to stop smoking and helps pave the way to better treatments for nicotine withdrawal symptoms. (For more information on these and other nicotine studies, see "Like Other Drugs of Abuse, Nicotine Disrupts the Brain's Pleasure Circuit.")

NIDA-supported researchers also are making excellent progress in identifying the molecular components of nicotine addiction. One recent study has pinpointed a particular protein in the brains of mice that is essential to the process of nicotine addiction. Mice that lack this protein will not self-administer nicotine. This suggests that the mice do not experience the rewarding effects of nicotine. This major discovery provides us with a very specific brain site to target in developing novel nicotine addiction treatment medications.

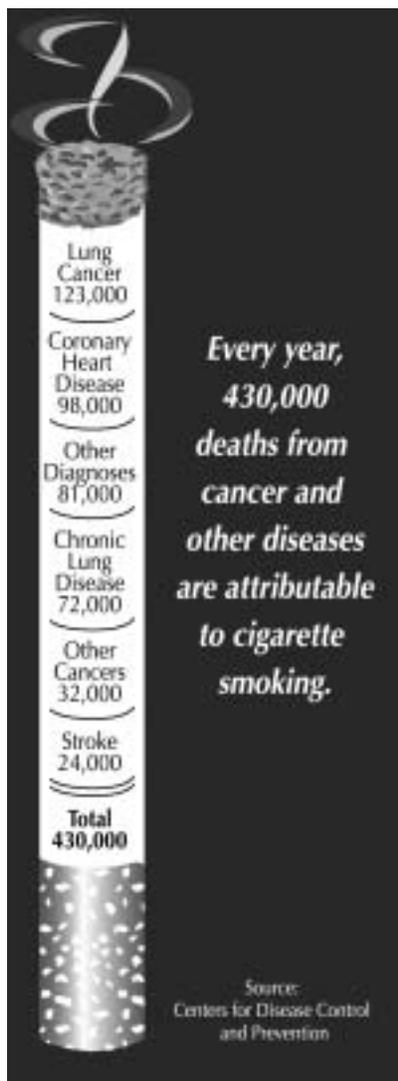
Although nicotine addiction lies at the root of tobacco use, another recent study by scientists using sophisticated brain imaging technology suggests that, in addition to nicotine, some unknown compound in cigarette smoke also raises dopamine levels in smokers' brains by inhibiting an enzyme that breaks down dopamine. If further research confirms that smoking alters dopamine levels through multiple mechanisms, it would open the door to new approaches to developing effective smoking treatment medications (see "Tobacco Smoke May Contain a Psychoactive Ingredient Other Than Nicotine").

Ultimately, the best treatment for nicotine addiction is prevention. Here, too, a long history of NIDA-supported

research has given us the tools to develop effective drug abuse prevention approaches, including strategies to prevent tobacco use. We have distilled this scientific base for

drug abuse prevention in the first-ever research-based guide for preventing drug abuse. The principles in this guide, "Preventing Drug Use Among Children and Adolescents," can be applied by families, schools, and communities to prevent adolescents from beginning to use tobacco and other harmful drugs (see "NIDA Materials to Help Communities Develop Drug Abuse Prevention Programs," V12-6, November/December 1997).

Never before has the momentum for addressing the public health problem posed by tobacco use been greater. To accelerate this momentum, NIDA, in collaboration with the Robert Wood Johnson Foundation, the National Cancer Institute, and the Centers for Disease Control and Prevention Office on Smoking and Health, is holding a scientific conference on nicotine addiction on July 27-28, 1998, in Bethesda, Maryland. The conference, called "Addicted to Nicotine: A National Research Forum," brings together the leaders in nicotine addiction research to share knowledge, identify gaps in that knowledge, and point us toward promising new areas of research. Ultimately, it is that research that will make possible a future in which no more lives are lost to what is ultimately a preventable, and, if not prevented, treatable disease. **NN**



Like Other Drugs of Abuse, Nicotine Disrupts the Brain's Pleasure Circuit

By Neil Swan, *NIDA NOTES* Staff Writer

All drugs of abuse disrupt the normal flow of the neurotransmitter dopamine, stimulating its release and increasing its brain levels. This action is believed to be significantly involved in producing drug-induced feelings of pleasure and reward and, over time, addiction and vulnerability to withdrawal symptoms. Drugs of abuse begin this action by chemically binding to specific molecular sites called receptors, some of which are found on dopamine nerve cells.

Recent findings from several NIDA-funded researchers confirm not only that nicotine is highly addictive but that it affects the same brain mechanism as other drugs of abuse and increases brain levels of dopamine. The findings also suggest how nicotine abstinence and withdrawal activate the body's stress systems. Two research teams have spotlighted how nicotine, just like heroin or cocaine, activates dopamine-containing nerve cells in the brain's mesolimbic system, which is involved in emotion and behavior. Another group has shown that some brain changes during withdrawal from chronic nicotine use are similar to those that occur during withdrawal from other drugs of abuse.

Dr. John A. Dani of Baylor College of Medicine in Houston and his colleagues have shown that nicotine binds at multiple receptors on dopamine nerve cells, or neurons, to activate the neurons. Theoretically, this activation of dopamine neurons by nicotine begins the response that leads to feelings of pleasure and reward, and then addiction. The researchers examined dopamine nerve cells from the brains of rats that had been exposed to nicotine for prolonged periods. They found that nicotine at levels comparable to those found in human smokers first activates or sensitizes these neurons but then quickly desensitizes them.

The researchers believe nicotine-induced desensitization of dopamine cells may explain why smokers report that they rapidly become tolerant to the effects of smoking during the day. The tolerance fades overnight so that by the next morning the dopamine cells are resensitized to nicotine, the researchers theorize.

"This finding suggests a cellular explanation for smokers' reports that their first cigarette of the day is the most pleasurable," while the pleasurable effect of cigarettes smoked later in the day is greatly reduced, says Dr. Dani. "It's a

biophysical extrapolation to explain how the cellular response to nicotine ultimately affects behavior," he explains. The results further support the theory that nicotine acts through the same cellular mechanism as other addictive drugs and that this mechanism—dopamine activity in the mesolimbic system—is implicated in various ways in the cellular and behavioral effects of addictive drugs, he says.

Dr. Marina Picciotto of Yale Medical School in New Haven, Connecticut, and her colleagues in France, Sweden, and Switzerland have gone a step further and have pinpointed the specific protein to which nicotine binds on a particular nicotinic receptor on a dopamine cell.

The researchers used a strain of mouse developed by Dr. Picciotto in which the gene that encodes this protein is eliminated or "knocked out." The researchers found that these knockout mice did not self-administer nicotine as their normal sisters did. The finding suggests that the mice without the protein, called the beta 2 subunit, did not experience the normal reinforcing, or rewarding, effects of nicotine. But the mice did self-administer cocaine, an indication that knocking out the beta 2 subunit affected only their response to nicotine, not to other drugs.

The experiment tested the behavioral response of the mice. But what about their physiological response? If the knockout mice were injected with nicotine, would the nicotine increase dopamine levels? No. In a followup experiment, nicotine injections did not boost dopamine levels in the brains of knockout mice. This finding provided further evidence of the influential role of the beta 2 subunit in the nicotine addiction process. The study findings are consistent with the theory that the dopamine brain circuit is the reward pathway used by all drugs of addiction but that different drugs activate this pathway through different molecular gateways.

"In our altered mice, we've shown that if you take away one subunit of the nicotinic receptor, you take away the ability of nicotine to stimulate dopamine release," explains Dr. Picciotto.

"To actually pinpoint a particular protein shown to be critical to nicotine addiction is a major discovery," says

NIDA Director Dr. Alan I. Leshner. Future medications for nicotine addiction might target that specific protein, he says.

Dr. Picciotto is now studying how this nicotinic receptor and its subunits affect the rewarding properties of other drugs such as morphine, cocaine, and alcohol. "People who abuse other drugs are also likely to be smokers, and we would like to know more about interactions between the different systems that mediate the rewarding effects of these different drugs," she says.

Another NIDA-funded study shows that the severity of changes that occur in the brain's pleasure circuits during withdrawal from chronic nicotine use rivals that experienced during withdrawal from other abused drugs such as cocaine, amphetamine, morphine, and alcohol.

The study found dramatically decreased sensitivity to pleasurable electrical stimulation in the brains of rats after nicotine administration was stopped. The decreased sensitivity, which lasted several days, may correspond to the depression experienced by humans who quit smoking "cold turkey."

"Understanding these decreases in the brain's sensitivity to pleasurable stimulation during nicotine abstinence helps explain why it's so hard for people to stop smoking and may help develop better treatments for nicotine withdrawal symptoms such as depression, anxiety, irritability, and craving for a cigarette," says Dr. Leshner. "The brain-change similarities to other drugs of abuse emphasize that there are common characteristics to withdrawal from all addictive substances, one of which is decreased sensitivity to pleasure," he says.

Dr. Athina Markou and her colleagues at The Scripps Research Institute in La Jolla, California, measured the effects of nicotine abstinence on the brain's sensitivity to pleasure-inducing electric pulses. They taught rats to self-administer brief electrical pulses in the lateral hypothalamus, part of the brain's reward circuitry, and then monitored the level of pleasure, or reward, experienced by the animals.

Reward sensitivity measures were taken during and after administration of nicotine. For a week the rats were infused with a steady dose of nicotine to produce nicotine blood levels equivalent to those of a human smoking 30 cigarettes a day.

While nicotine was administered, the animals' sensitivity to brain reward remained stable, as shown by the fact that they self-administered pleasure-inducing pulses at the same level as before nicotine was introduced. When the rats' nicotine was cut off, however, the scientists had to increase the intensity of electrical current by more than 40 percent before the rats showed through their behavior that electrical pulses to the brain were again pleasurable.

"These results are comparable to the altered brain reward sensitivity found during withdrawal from many other addictive drugs," says Dr. Markou. The experiment provides a valid animal model for studying the function of brain reward circuits involved in nicotine withdrawal and to help develop treatments for nicotine addiction, she adds.

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Tobacco Smoke May Contain a Psychoactive Ingredient Other Than Nicotine

Nicotine may not be the only psychoactive component in tobacco smoke, according to a study funded in part by NIDA. Using positron emission tomography, an advanced neuroimaging technology, Dr. Joanna S. Fowler and her colleagues at Brookhaven National Laboratory in Upton, New York, have produced images showing that smoking decreases the brain levels of an important enzyme that breaks down the neurotransmitter dopamine. The amount of the enzyme, called monoamine oxidase (MAO), is reduced by 30 to 40 percent in the brains of smokers, compared to nonsmokers or former smokers, the brain scans show. The reduction in brain MAO levels may result in an increase in levels of dopamine, which scientists associate with the reinforcing effects of drugs of abuse.

Although nicotine causes increases in brain dopamine, it does not affect MAO levels, research has shown. Thus it appears that another component of tobacco smoke is inhibiting MAO. "Whatever is inhibiting MAO could be acting in concert with nicotine to enhance dopamine's activity by preventing its breakdown," says Dr. Fowler.

The concept that the smoking-related reduction of MAO activity may synergize with nicotine's stimulation of dopamine levels to produce the diverse behavioral effects of smoking suggests that MAO inhibitor drugs may be useful as an additional therapy in smoking cessation efforts, she adds. MAO inhibitor drugs are used to treat depression and Parkinson's disease. One such drug, moclobemide, is already being used experimentally to assist persons trying to quit smoking.

Dr. Fowler's research was funded by NIDA, the National Institute of Neurological Diseases and Stroke, and the Department of Energy's Office of Health and Environmental Research.



The lighted areas in these brain images show levels of an enzyme called monoamine oxidase (MAO). A marked decrease in MAO is apparent in the brains of smokers compared to those of non-smokers, but nicotine is not responsible.

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Facts About Nicotine and Tobacco Products

About 62 million people in the United States ages 12 and older, or 29 percent of the population, are current cigarette smokers, according to the 1996 National Household Survey on Drug Abuse. This makes nicotine, the addictive component of tobacco, one of the most heavily used addictive drugs in the United States.

Effects of Nicotine

When a person inhales cigarette smoke, the nicotine in the smoke is rapidly absorbed into the blood and starts affecting the brain within 7 seconds. In the brain, nicotine activates the same reward system as do other drugs of abuse such as cocaine or amphetamine, although to a lesser degree. Nicotine's action on this reward system is believed to be responsible for drug-induced feelings of pleasure and, over time, addiction. Nicotine also has the effect of increasing alertness and enhancing mental performance. In the cardiovascular system, nicotine increases heart rate and blood pressure and restricts blood flow to the heart muscle. The drug stimulates the release of the hormone epinephrine, which further stimulates the nervous system and is responsible for part of the "kick" from nicotine. It also promotes the release of the hormone beta-endorphin, which inhibits pain.

People addicted to nicotine experience withdrawal when they stop smoking. This withdrawal involves symptoms such as anger, anxiety, depressed mood, difficulty concentrating, increased appetite, and craving for nicotine. Most of these symptoms subside within 3 to 4 weeks, except for the craving and hunger, which may persist for months.

Health Effects of Tobacco Products

Besides nicotine, cigarette smoke contains more than 4,000 substances, many of which may cause cancer or damage the lungs. Cigarette smoking is associated with coronary heart disease, stroke, ulcers, and an increased incidence of respiratory infections. Smoking is the major cause of lung cancer and is also associated with cancers of the larynx, esophagus, bladder, kidney, pancreas, stomach, and uterine cervix. Smoking is also the major cause of chronic bronchitis and emphysema.

Women who smoke cigarettes have earlier menopause. Pregnant women who smoke run an increased risk of having stillborn or premature infants or infants with low birthweight. Children of women who smoked while pregnant have an increased risk for developing conduct disorders.

Cigar and pipe smokers and users of chewing tobacco and snuff can also become addicted to nicotine. Although cigar and pipe smokers have lower death rates than cigarette smokers do, they are still susceptible to cancers of the oral cavity, larynx, and esophagus. Users of chewing tobacco and snuff have an elevated risk for oral cancer.

Treatment

Like addiction to heroin or cocaine, addiction to nicotine is a chronic, relapsing disorder. A cigarette smoker may require several attempts over many years before that person is able to permanently give up smoking. Less than 10 percent of unaided quit attempts lead to successful long-term abstinence. However, studies have shown significantly greater cessation rates for smokers receiving interventions compared to control groups who do not receive the interventions. Interventions that involve both medications and behavioral treatments appear to show the most promise.

The primary medication therapy currently used to treat nicotine addiction is nicotine replacement therapy, which supplies enough nicotine to the body to prevent withdrawal symptoms but not enough to provide the quick jolt caused by inhaling a cigarette. Four types of nicotine replacement products are currently available. Nicotine gum and nicotine skin patches are available over the counter. Nicotine nasal spray and nicotine inhalers are available by prescription. On average, all types of nicotine replacement products are about equally effective, roughly doubling the chances of successfully quitting.

Another medication recently approved by the Food and Drug Administration as an aid for quitting smoking is the antidepressant bupropion, or Zyban. The association between nicotine addiction and depression is not yet understood, but nicotine appears to have an antidepressant effect in some smokers. Paradoxically, though,

bupropion is more effective for treating nicotine addiction in nondepressed smokers than in smokers who are depressed.

For More Information

More information about nicotine addiction and tobacco can be found at the NIDA Web site at

<http://www.nida.nih.gov>, or by calling Infofax, NIDA's automated information retrieval system, at 1-888-NIH-NIDA. Information is also available from the National Clearinghouse for Alcohol and Drug Information (NCADI), P.O. Box 2345, Rockville, MD 20847-2345, (800) 729-6686. The NCADI Web site is <http://www.health.org>. **NN**

NIDA-Supported Research Shows. . .

Promising Advances Toward Understanding the Genetic Roots of Addiction

By June R. Wyman, NIDA NOTES Staff Writer

This is the second article in a new series, "NIDA-Supported Research Shows," that will appear periodically in NIDA NOTES. The series will explain broad scientific concepts in drug abuse research and describe how NIDA researchers are using these concepts to develop more effective ways to prevent and treat drug abuse and addiction. The first article, "Rate and Duration of Drug Activity Play Major Roles in Drug Abuse, Addiction, and Treatment," appeared in NIDA NOTES, March/April 1997.

At a major scientific meeting, a scientist announced to a spellbound audience that he had identified some of the genes associated with drug abuse. He described the mutations in those genes that lead people to abuse marijuana, heroin, cocaine, and other drugs. His landmark discovery brought scientists a giant step closer to dramatically curbing drug abuse. Although some drug abuse researchers are predicting this tale could come true as early as the next 5 to 10 years, for now it is fiction.

Currently, scientists agree that genetics is involved in drug abuse, but the consensus ends there. Many genes are thought to act together to make someone more likely to abuse drugs. But exactly which genes those are and what they do are the subject of a lively scientific debate. Further, since drug addiction appears to be the product of both heredity and environment, the roles of the two are hard to separate.

At NIDA, a Genetics Workgroup is trying to sort out these issues. The group's mission is to assess the state of the science, identify research gaps, and decide what studies are needed to untangle the genetic roots of addiction. Its members consult with experts from around the country to get advice on what directions NIDA should take, according to Dr. Jonathan Pollock of NIDA's Division of Basic Research, who chairs the group.

Meanwhile, amid the debate, new scientific information is emerging, giving scientists leads that may generate new strategies for drug abuse prevention and treatment.

Family Resemblances

Whether or not someone feels good after smoking marijuana is strongly influenced by heredity, report NIDA-funded grantees from Harvard Medical School. Their conclusion comes from a study of 352 pairs of identical male twins and 255 pairs of fraternal male twins, all of whom had smoked marijuana more than five times in



Identical twins have exactly the same genes. Scientists study twins to look for the genetic basis of disorders such as drug abuse.

their lives. Identical twins have exactly the same genes, while in fraternal twins about half the genes are identical.

Dr. Ming Tsuang, Dr. Michael Lyons, and their colleagues compared the identical twins' answers with the fraternal twins' answers to a set of questions about how good or bad they felt after smoking marijuana. The identical twins' answers were significantly more alike than those of the fraternal twins. The researchers interpret their data to mean that genetic factors have a significant impact on whether someone will enjoy marijuana.

It is this kind of research that begins the search for drug abuse genes. Although studies of twins and families cannot pinpoint specific genes related to drug addiction, they can look closely at people who share a drug abuse disorder and a common genetic makeup. "Twin studies are promising because they ask exactly what is heritable," says Dr. Harold Gordon of NIDA's Division of Clinical and Services Research. Then, using blood samples, molecular biologists can examine these individuals' genetic material, or DNA, to locate shared genetic characteristics, he says.

To advance such work, NIDA has expanded funding to epidemiologists who work with large numbers of twins or families but have not previously studied addiction to drugs other than nicotine and alcohol. For example, Dr. Kenneth Kendler of Virginia Commonwealth University in Richmond has been studying the genetic basis of nicotine dependence in a large database of twins and siblings in Virginia. NIDA's support has allowed him to launch an epidemiologic survey of those twins that will flag vulnerability to a wide range of drugs including nicotine, cocaine, barbiturates, opiates, inhalants, and marijuana. To measure gender differences, he is doing separate analyses of female/female twins and male/male twins.



NIDA's Dr. George Uhl examines a gene that codes for a type of dopamine receptor—a molecule to which the brain chemical dopamine attaches itself. The inset shows a particular gene from nine different people; each column represents one person. Columns 6 and 9, which have two dark blots, are genetically different from the others. Researchers are trying to determine whether genetic differences such as these relate to drug abuse.

Dr. Roy Pickens of NIDA's Division of Intramural Research (DIR) in Baltimore, with colleagues at Johns Hopkins University in Baltimore and the University of Minnesota in Minneapolis, also has been studying twins. Their study looked at same-sex twins, half identical and half fraternal, with coexisting, or comorbid, drug addiction, alcohol abuse, and/or mental health problems. The researchers' analyses suggest that common genetic factors are involved in drug and alcohol abuse and certain psychological disorders in men. They speculate that this may account for some of the comorbidity among these disorders. Genetic influences were not identified in women, probably because there were not enough women in the study, says Dr. Pickens.

Likely Candidate Genes

Meanwhile, geneticists are homing in on particular drug abuse genes—a daunting task, given that humans have around 100,000 genes and, of those, more than 40,000 may be expressed in the brain, where drugs of abuse act. Still, many scientists are optimistic. "We've known for a long time that genetics is an important part of an individual's response to drugs of abuse," says Dr. John Crabbe, a NIDA grantee at Oregon Health Sciences University in Portland. "What we're able to do now is get our hands on specific candidate genes."

Of particular interest are genes that control the brain chemical dopamine, which is associated with movement and pleasure, including pleasure from drug use. "Genes in the dopamine circuit are likely candidates, and most of

these have been examined at least to some degree," says Dr. George Uhl, chief of DIR's Molecular Neurobiology Branch. This work is being done in mice, which have critical genetic similarities to humans. Also, scientists know more about the genetic makeup of mice than that of any other mammal except humans.

One approach to studying the genes that may influence drug responses is to remove, or "knock out," a candidate gene in mice and see what happens. For example, DIR Scientific Director Dr. Barry Hoffer and scientists from two Swedish laboratories recently used genetic engineering techniques to knock out the gene for a protein called Nurr1. The brains of these mice lacked the two major groups of dopamine neurons and, thus, could not produce any dopamine.

The scientists conclude that in mice Nurr1 is critical for normal development of dopamine-containing nerve cells, and they speculate that development of those cells may be abnormal in people who are vulnerable to substance abuse. "These people may be abusing drugs in an attempt to counteract the deficiency," says Dr. Hoffer, who did the study with scientists from the Karolinska Institute and the Ludwig Institute for Cancer Research, both in Stockholm.

"Medications could be developed that interact with Nurr1 and thus regulate dopamine levels in the brain," Dr. Hoffer speculates. "These medications could be useful in treating an underlying disorder that might make some people more likely to abuse drugs."

Another approach to studying the genetics of addiction is to study responses to drugs in genetically identical strains of mice. At Oregon Health Sciences University and the Portland Veteran's Administration Medical Center, Dr. Crabbe and Dr. John K. Belknap have studied more than 25 strains of these inbred mice. "There are big differences among strains in whether they self-administer different drugs," Dr. Crabbe observes. For example, a strain called DBA/2 refuses most drugs of abuse, while C57BL/6 mice seem to like almost everything, including alcohol, morphine, cocaine, phenobarbital, and diazepam. Other inbred strains fall between these extremes. "This work shows that specific genes cause animals to like particular drugs, so that vulnerability to drug abuse is partly under genetic control," says NIDA's Dr. Pollock.

So the evidence from animal studies is compelling. But finding equally strong evidence in humans for a genetic influence on drug addiction has proved trickier. Although a number of genes have been implicated, none has been clearly linked to drug addiction.

At DIR, Dr. David Vandenberg, Dr. Uhl, and their coinvestigators are looking for genes that may be involved in drug abuse by comparing DNA from drug abusers to that of people who do not abuse drugs. So far the strongest candidate is a variant of a gene that tells the body to produce an enzyme called COMT (catechol-o-methyltransferase). Widespread throughout the body, this enzyme helps break down and inactivate dopamine and related substances. COMT occurs in two genetically determined forms: low activity and high activity. "We found that the high-activity forms of the gene and the enzyme are found more often in drug abusers," Dr. Vandenberg says. If further work confirms this finding, then drugs that lower COMT activity could be tested as treatments for drug addiction, he says.

Gene Hunters

What will it take to locate the particular genes involved in human drug addiction? Some scientists think that the best bet is what scientists call a genome-wide scan. This method, which was recently used to identify the genetic defect for Parkinson's disease, entails several steps:

- find families with high rates of the disorder;
- analyze blood samples from these people to locate the genetic markers, or stretches of DNA, that family members with the disorder seem to share that are different from those who do not have the disorder;
- scan all known human genes using sources such as the National Institutes of Health's Human Genome Project, and try to find some connection—for example, a gene on the chromosome that is known to regulate dopamine levels; and
- go back to the blood samples to look for shared mutations in those genes.

But applying this method to drug addiction will not be straightforward. "What should we look at? Drug abuse per se? Sensation seeking? Specific biological markers? We really don't know," says Dr. Gordon.

"These genes could operate in many ways. They might make you seek sensations or make it hard to withdraw once you start abusing drugs or make you get higher than other people. Or maybe you need all of these to become a drug abuser," says Dr. Pickens.

Dr. Crabbe in Portland is one of those researchers who thinks that identifying some of the genes involved in drug abuse and addiction is in sight. "That's the big thing that will happen in this field in the next 5 to 10 years. We'll turn the theory that genes influence addiction into the identification of specific genes," he predicts.

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Women's Dependence on Smoking Affected By Something in Addition to Nicotine

By Neil Swan, NIDA NOTES Staff Writer

A number of studies have shown that women find it more difficult than do men to quit smoking cigarettes. This is especially evident in studies of nicotine replacement therapies that use nicotine patches or nicotine gum. Now two separate NIDA-funded studies examining gender differences related to smoking suggest that something in addition to nicotine is involved in women's dependence on smoking tobacco.

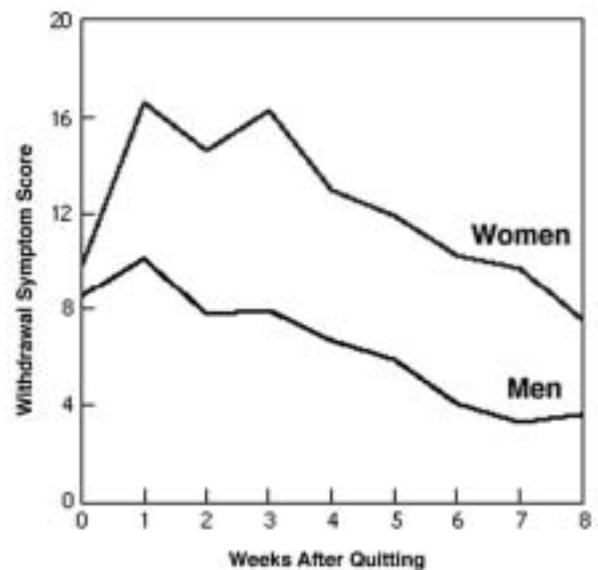
"It appears that, compared to men, women may smoke less for nicotine and more for nonnicotine effects of smoking," says Dr. Kenneth A. Perkins, a psychologist at the University of Pittsburgh Medical Center. These nonnicotine influences might include nondrug-induced sensory effects like seeing and smelling tobacco smoke, conditioned responses to these smoke stimuli, or social pleasures involved in smoking rituals, he suggests.

For example, one observer has noted that smokers may exhibit gender differences in the way they gather outside buildings to smoke, Dr. Perkins says. Male smokers tend to be loners; females tend to gather in social groups. These behaviors may indicate critical gender-based differences relating to tobacco smoking that may have little to do with nicotine, observers theorize. Dr. Perkins calls these nonnicotine influences "external stimuli."

If further research supports this view of gender differences in external and behavioral influences related to smoking, says Dr. Perkins, it will be important to revise smoking cessation treatments for women trying to quit. This would mean tailoring therapy for women to increase behavioral support and rely less on nicotine replacement.

Dr. Perkins reviewed scores of studies of smoking and its addictive properties and smoking cessation programs. He found that these epidemiological and clinical studies consistently show that while smoking is declining among Americans, it is not decreasing as rapidly among women as among men. If present trends continue, women smokers will outnumber men by the next decade, says Dr. Perkins. The research suggests that this is at least partly because of the greater difficulty women have in quitting. Women in the studies tend to be less successful in smoking cessation trials, especially those using nicotine replacement therapy.

Withdrawal Is Different for Women—Appetite, Craving Greater Than Men's



Women using nicotine gum therapy to quit smoking reported greater withdrawal symptoms than men did. The Withdrawal Symptom Score was calculated from self-reports of the degree to which study participants experienced symptoms such as craving for a cigarette, irritability, anxiety and tenseness, and excessive hunger. A high score represented greater symptoms.

Lower cessation rates for women could be expected if women smoked more cigarettes or inhaled more nicotine than did men. Both are indicative of nicotine dependence, and smokers who are more strongly nicotine-dependent often have greater difficulty quitting. But just the opposite appears to be the case, says Dr. Perkins. Women tend to smoke fewer cigarettes per day, to smoke brands with lower nicotine yields, and to be less likely to inhale deeply, compared to men, according to his research review. Thus, evidence indicates women smokers are less, not more, nicotine-dependent than are men.

Further support for the notion of additional, nonnicotine addiction factors comes from a study of gender differences

Compared to men, women may smoke less for nicotine and more for nonnicotine effects of smoking.

in the effects of different doses of nicotine gum on tobacco withdrawal symptoms. Dr. Dorothy Hatsukami, a psychiatry professor at the University of Minnesota, found that nicotine gum did not work as well to ease withdrawal symptoms for women trying to quit smoking as it did for men trying to quit. As in Dr. Perkins' review, her results seemed contrary to expectations. If women are more sensitive to or dependent on the effects of nicotine than are men, as their lower smoking cessation rates would suggest, then women should be more responsive than are men to nicotine replacement, she reasoned. But this was not shown in her data, which paralleled Dr. Perkins' findings. Women were less sensitive to the effects of nicotine, she says.

The lower cessation success with nicotine replacements in women compared to men may in part be attributed to this reduced effectiveness of the replacement therapy in relieving nicotine withdrawal symptoms. It also may indicate that something else is involved besides nicotine dependence, says Dr. Hatsukami. Like Dr. Perkins, she concluded that women may be more affected by other aspects of smoking.

What is the "something else"? In his review, Dr. Perkins examines alternative possibilities such as gender variations related to body weight or physiological effects of the 4,000 compounds found in cigarettes in addition to nicotine. He finds no strong evidence to support these or other alternative explanations for gender differences in responses to smoking or attempts to quit smoking, leading to his speculation on the role of nondrug, or external, factors.

One answer might lie in psychophysiology studies that compare men's and women's abilities to detect changes within their bodies, such as heart-beat rate fluctuations, explains Dr. Perkins. Women are consistently less able than are men to detect changes in heart rate when no external clues are provided, according to a research review published in 1995 by Southern Methodist University

scientists. But this gender difference narrows significantly when subjects are provided with an external context, or clue, for the internal changes, such as viewing a horror film.

Thus, external stimuli appear to be more important to women than to men. It can be theorized, then, that women may be less responsive to internal stimuli such as nicotine and more responsive to external stimuli such as the sight and smell of tobacco and its smoke, he says.

Dr. Perkins emphasizes that it is wrong to conclude that nicotine is not important in reinforcing tobacco smoking among women. Women clearly experience nicotine withdrawal symptoms, he says. "The point is that there may be relatively subtle—but very important—differences in the sources of reinforcement [reward] that tobacco smoking provides to women relative to men," he says.

Some observers have speculated on the role of external influences in gender differences related to the use of other abused drugs. Research with users of cocaine, heroin, and other drugs points up the significance of external drug-craving "cues" such as persons, activities, or locations associated with prior drug use. Are there critical gender differences in responses to these powerful craving cues?

More research is essential, says Dr. Perkins. For tobacco, more study is called for because studies of nonnicotine reinforcement may help develop more effective smoking cessation therapies for women, he says.

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Smoking Any Substance Raises Risk of Lung Infections

By Michael D. Mueller, NIDA NOTES Staff Writer

Smoking any substance—tobacco, marijuana, or "crack," a smokable form of cocaine—increases a smoker's risk of developing bacterial pneumonia and other infections of the lungs, according to the findings of drug abuse, smoking and health, and AIDS researchers.

Although some drugs seem to have specific damaging effects when smoked, smoking anything appears to damage or paralyze the cilia, the hair-like projections in the lungs that sweep out microbes and other matter that can cause disease, according to NIDA-funded studies.

Damaging the lung's cilia, the respiratory system's first line of defense, can have severe consequences for people with weak immune systems, the studies note.

A NIDA workshop held in August 1995 examined current research at that time on the cardio-pulmonary complications of crack cocaine use. In a report summarizing the major findings presented at the workshop, Dr. Pushpa V. Thadani, a pharmacologist in NIDA's Division of Basic Research, notes that smoking cocaine appears to weaken the crack smoker's natural resistance to infection in the lungs.

"Pulmonary alveolar macrophages—cells that protect the lungs from infectious agents—are exposed to the highest concentrations of cocaine," says Dr. Thadani. NIDA-funded studies show that alveolar macrophages from crack cocaine smokers are less active than are alveolar macrophages from nonsmokers in destroying *Staphylococcus aureus*, a common cause of bacterial lung infection. Preliminary findings also indicate that alveolar macrophages of cocaine smokers are more susceptible to HIV-related infections than are alveolar macrophages of people who do not smoke cocaine.

"Much remains unknown about the effects of crack smoking on the alveolar macrophages and other cells of defense in the lungs," says Dr. Thadani. "However, it appears that there are profound effects, and this needs to be further explored," she says.

Dr. Donald P. Tashkin, a professor of medicine at the University of California at Los Angeles School of Medicine, and his colleagues recently examined the effects

Smoking anything appears to damage or paralyze the cilia, the hair-like projections in the lungs that sweep out microbes and other matter that can cause disease.

that habitual smoking of tobacco, marijuana, and/or cocaine has on the lining of the lung's air passages. The NIDA-funded study included 53 nonsmokers, 14 smokers of crack cocaine only, 40 smokers of marijuana only, and 31 regular tobacco smokers. In addition, there were 16 smokers of both cocaine and marijuana, 12 smokers of cocaine and tobacco, and 44 smokers of both marijuana and tobacco. Thirty-one patients smoked all three substances.

The researchers found that smoking either marijuana or tobacco produces significant damage to the cilia in the lining of the airways. Among smokers of both marijuana and tobacco, it appears that the effects of marijuana add to the effects of tobacco, and vice versa. "The damage to the ciliated cells in the lining of the airways caused by smoking tobacco, and/or marijuana weakens the ability of the lungs to remove inhaled particles, making the lungs more vulnerable to infection," says Dr. Tashkin.

Cocaine smokers had fewer significant abnormalities than marijuana or tobacco smokers did—but more abnormalities than were detected among nonsmokers, Dr. Tashkin says. Among people who smoke both tobacco and cocaine, cocaine smoking appears to produce injury to the mucosal lining of the airways beyond that caused by smoking tobacco alone.

A NIDA-supported study by Dr. Waleska T. Caiaffa and her colleagues at Johns Hopkins University in Baltimore compared the medical records of 40 HIV-positive injecting drug users (IDUs) who had suffered from one bout of bacterial pneumonia with those of 197 HIV-positive IDUs with no history of bacterial pneumonia. The study found that HIV-positive IDUs who smoked illicit drugs were almost twice as likely to develop bacterial pneumonia as were their counterparts who did not smoke illicit drugs. This association was independent of age, degree to which the natural immune system had been suppressed, and cigarette smoking. Among the 77 HIV-positive IDUs who reported smoking drugs, 87.9 percent indicated that they had smoked marijuana, 25.9 percent said that they had used cocaine, and 9.1 percent admitted smoking crack.

Smoking is a serious issue among AIDS patients, according to several NIDA-supported studies. The health effects of smoking illicit drugs are above and beyond those caused by smoking cigarettes, the studies note. People with AIDS often die of pneumonia and other lung problems, and smoking tobacco and/or illicit drugs increases the risks for these diseases.

"The effect that smoking has on the lungs is more serious than most people realize. Smoking anything is bad for your health, especially if your immune system has been weakened," says Dr. Tashkin.

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Daughters of Mothers Who Smoked During Pregnancy are More Likely to Smoke, Study Says

By Robert Mathias, NIDA NOTES Staff Writer

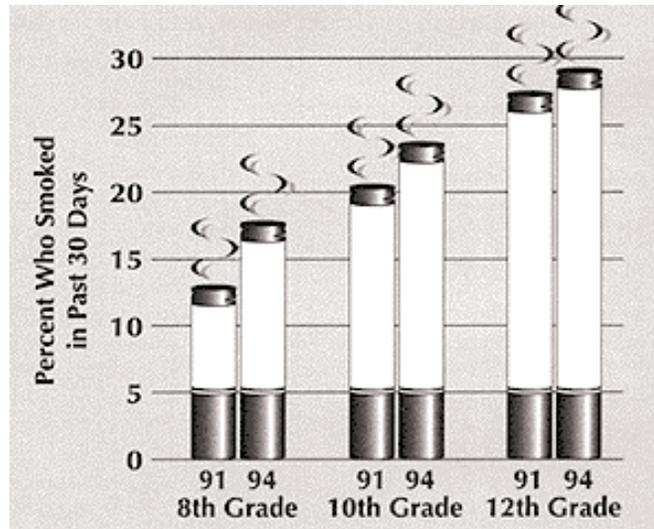
Researchers have long wondered about the impact of prenatal exposure to drugs on a child's vulnerability to drug abuse. Now, NIDA-funded studies have documented a relationship between prenatal exposure to nicotine and adolescents' use of tobacco. Dr. Denise Kandel of Columbia University found that daughters of women who smoked cigarettes while they were pregnant are four times more likely to begin smoking during adolescence and to continue smoking than daughters of women who did not smoke during pregnancy.

"The clearest message from the study is that mothers should not smoke during pregnancy," says Dr. Kandel. The study suggests that nicotine, which crosses the placental barrier, may affect the female fetus during an important period of development so as to predispose the brain to the addictive influence of nicotine more than a decade later, she says.

Prenatal smoking by these mothers did not have a strong effect on their sons' smoking, but it is not clear why, says Dr. Kandel. Male hormones or structural differences of male and female brains may protect the developing male fetus from the nicotine entering the brain, she says, but notes, "That is all very speculative."

Prenatal exposure to smoking has previously been linked with impairments in memory, learning, cognition, and perception in the growing child, says Dr. Jagjitsing Khalsa of NIDA's Division of Clinical and Services Research. The results of Dr. Kandel's study suggest that smoking during pregnancy may create a risk of early and continued smoking among these women's children, he says. Noting that other NIDA researchers are looking at the possible intergenerational transmission of a tendency to use marijuana

Trends in Adolescent Girl's Current Use of Cigarettes



According to NIDA's Monitoring the Future Study, the percent of adolescent girls who smoke cigarettes has increased in the last 4 years. Although smoking among adolescent girls has been linked to many different factors, Dr. Kandel's study is the first to document a possible link between prenatal exposure to nicotine and an adolescent girl's tendency to smoke cigarettes.

through prenatal exposure, Dr. Khalsa says, "We need to let women know that if they take drugs during pregnancy they may put their offspring at risk for future drug use."

In previous research, Dr. Kandel had examined the intergenerational effects of drug use by following a cohort of New York State adolescents who were periodically reinterviewed over the course of 19 years. That research indicated that a mother's cigarette smoking had a greater effect than a father's on smoking among both sons and daughters. When analyses of different social influences could not identify the reason for this maternal effect, Dr. Kandel focused on one factor that

differentiated mothers from fathers—a mother's smoking during pregnancy.

In her most recent study, Dr. Kandel analyzed followup interview data on 192 mothers and their first-born adolescents from the New York State study. The children's mean age was 12 1/2. The analysis revealed that 26.4 percent of girls whose mothers smoked while pregnant had smoked in the last year. By comparison, only 4.3 percent of girls who were not prenatally exposed to nicotine had smoked in the last year. While more prenatally exposed boys had also smoked in the last year compared with boys whose mothers had not smoked during pregnancy, the difference was not statistically significant.

Subsequently, Dr. Kandel replicated her New York State analysis with pre- and postnatal smoking data on 797 mothers and their children drawn from the National Longitudinal Survey of the Work Experience of Youth Cohort, a Bureau of Labor Statistics survey that has been conducted annually since 1979. The second analysis

confirmed the findings from the New York State survey, says Dr. Kandel. The combined data from both surveys indicated a fourfold greater risk of smoking for girls whose mothers smoked during pregnancy.

To ensure that it was a mother's prenatal smoking and not her postnatal smoking that affected her daughter's smoking, the researchers analyzed the impact of those mothers' smoking both during and after pregnancy. They found that, regardless of the amount or duration of current or past maternal smoking, the strongest correlation between maternal smoking and a daughter's smoking occurred when the mother smoked during pregnancy.

Smoking activates several brain neurotransmitter systems including the dopamine system, which is involved in the reinforcing effects of addictive drugs in general, points out

Dr. Kandel. Since this study raises the possibility that nicotine may modify the developing fetus's dopamine system, making it more susceptible to the effects of nicotine at a later time in life, "The children whose mothers smoked during pregnancy are not only going to be more likely to smoke, but also may be more likely to use and become dependent on other drugs," she predicts. Dr. Kandel hopes to research this issue by following the adolescents in her study for another 6 years.

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